Robust methods of analysing repeated measurements data in a longitudinal setting.

SHANBHAG, Sharayu.

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REFERENCE

ROBUST METHODS OF ANALYSING REPEATED MEASUREMENTS DATA IN A LONGITUDINAL SETTING

Sharayu Shanbhag

ROBUST METHODS OF ANALYSING REPEATED MEASUREMENTS DATA IN A LONGITUDINAL SETTING

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DECLARATION

I declare that the following dissertation embodies the results of my special study, that the dissertation is my own composition, and that it has nor previously been presented in application for a higher degree or any other professional qualification.

ABSTRACT

Two longitudinal data sets were individually analysed within this thesis. Data set A was a vital signs data set and data set B was a data set of dietary response. Initially, an exploratory data analysis approach was used to analyse the data at each univariate time point. Missing data were observed and an approach was suggested of estimating some of these missing records. It was found that this missing data only affected multivariate test results when the proportion of individuals with missing records was large. While using the conventional methods of analysis of the data set as a whole, some authors suggest using restrictive covariance structures corresponding to the data, following the assumption of normality. An issue that can cause problems with matrix calculations for any multivariate method and therefore invalidates the multivariate procedures is if the number of repeated measures is greater than the number of individual profiles per group. In this situation there is the problem in assuming a normal distribution for the data, which is a major assumption for any multivariate analysis, when this assumption does not really hold. The main aim of our research was to devise methods of analysing the whole data set when the data is of the form mentioned above and when the assumption of normality fails. Various data reduction approaches were suggested for analysing the data in a multivariate manner for this situation. The following three approaches were suggested to reduce the number of repeated measurements: (a) multivariate summary measures, (b) principal components and (c) averaging the data over groups of time points.

Both the principal components and summary measures approaches do not retain the time element and so firm conclusions can not be made. Our main contribution, within this thesis, is to illustrate that there are ways of reducing the data by still retaining the element of time in some manner. This is by using the method of averaging the data over groups of time points. The suggested procedures, of averaging data over segments of time, allows the use of the usual multivariate tests and modelling procedures without having to meet the assumption of normality or having any constraints on the covariance structure. This reduction method leads to more robust tests. Most analysis of variance tests become reduced to Chi-squared tests following this type of data reduction approach.

Any statistical analyses were conducted with the aid of SAS 6.10 on VAX and later on 6.12 on UNIX. Data set A was the primary data set for analysis purposes.

INTRODUCTION

So far in the literature to date there have been a vast number of methods and applications used in the analysis of repeated measures data. The topic of 'Repeated Measures Data Analysis' is an expanding field and one in which there is a range of both new and old literature. There is also a wide variety of varying opinion on the way that repeated measures data should be analysed. Hence, it is not possible to compile a summary based on just methods used in literature so far. Instead, our research looks into some of the most common methods of analysis of repeated measures data (particularly for longitudinal research) which have been suggested until now. We look into some of the available literature in the areas of 'repeated measures' and 'profile data' analysis with particular attention focussed on the sorts of data obtained from 'longitudinal trials'. In our research we will be looking at biomedical data. However, repeated measures data can also arise in a wide variety of other contexts. Other research areas include agricultural, psychological, economic and social research.

Chapter 1 describes clearly what repeated measures are, shows the general structure of a longitudinal data set and suggests ways of obtaining such data. Both an ideal situation and a messy situation are described in order to give an idea of the shortcomings of such data. Specifically mentioned are the problems of missing data, unscheduled visits, non-balanced data, early dropouts and unequal spacing between visits. Ideas are suggested on how to control some of these problems but it must be noted that some of these suggestions are not always practical. Details are given on study design used to obtain repeated measure data. Through our research we have discovered that there are three general methods of collecting any type of data. These are through setting up a designed experiment, conducting a survey or with an observational study [40]. All three methods mentioned are very different in their approaches. However, the information being gathered using any of these methods would be similar whichever is used. The choice of using a particular method is up to the individual carrying out the study or the investigator. Factors, which may affect the choice of designs, would be things such as cost, efficiency, convenience and availability. It is believed that repeated measures data are usually obtained via some type of designed or planned experiment. There are four study designs that specifically lead to the measurement of repeated measures data [36]. These are split plot designs, crossover studies, source of variability studies and longitudinal studies. A study using any combination of these four designs would also yield repeated measures data.

Chapter 2 reviews some common methods used to analyse repeated measures or particularly longitudinal data. Distributional assumptions are also described in this chapter.

Chapter 3 describes the two longitudinal data sets A and B. Data set A was a 'large' longitudinal unbalanced data set which had three variables (Heart Rate, Systolic Blood Pressure and Diastolic Blood Pressure) that were measured for 86 patients who were from 2 centres and were each randomly allocated to one of four treatment groups (1 to 4). The three vital signs were each measured at multiple time points (at baseline and then over 24 hours at hourly intervals) per individual using an ambulatory measurement device. Normal ranges for vital signs and other categories were obtained from National Blood Pressure Education Program, JNCV Report and also from private communication with an M.D [69]. These categories were used to further classify data set A to obtain a categorical data structure. Data set B was a 'small' longitudinal balanced data set measured for 24 individuals that were randomly allocated to one of three diet groups (1 to 3). The readings were taken at baseline and also at 9 other on therapy time points. This data set had no categorical information available. These two data sets A and B were each analysed in an appropriate manner.

In the past, it has been recommended to use individual univariate tests at each time point to avoid the difficulties associated with multivariate analysis methods due to the fact that they can at times become quite tedious or complicated. Nowadays, with computers and computer packages such as SAS and S-Plus etc., the issue of problems with computation of multivariate methods is not of so much of a problem as it was in the past. In the existing literature many authors [19,30] disregard these univariate methods over time, claiming that they are not worth while. This is mainly because of dependence between successive measurements and difficulty in interpreting the various individual test results. Only the univariate approach of 'Response Features Analysis' is a method that is still considered to be worthwhile by various authors [19,20,43]. It was therefore decided to use only this univariate approach to summarise the data over time.

Initially an exploratory data analysis was conducted on the data and these findings are displayed in chapter 4. There was the problem of missing data that was encountered during data analysis. Thirteen of the 86 records from data set A and 4 of the 24 records from data set B had at least one missing 'on treatment' record. Section 4.2 briefly introduces the reader to the area of missing data, suggests some commonly used methods and describes an ad-hoc missing data generation process that was devised, to deal with the missing data issue, for the purpose of this thesis. The method was applied to data set A to

obtain a data set that contained 84 records of complete 'on treatment' information with 2 patients still having missing baseline information. It was felt that data generation was reasonable for data set A since it was very large and the time points were close together and there were many time points for each patient. It was believed that losing 2 patients worth of data out of 86 records at the start of the study would not affect the results that drastically for any univariate or multivariate time dependent methods applied to this particular data set. When analysing the smaller data set B, only 4 of 24 individuals had at least one missing record. Following the data generation method, there were 22 individuals remaining with a full set of records but the data set would now become unbalanced. Since the data set was smaller than data set A and the time points were further apart, we were uncertain of whether the data generation method would be appropriate for data set B.

In order to get a feel for what was going on with the data and how the data generation method would affect any results, both the old data sets (with missing records) and the new data sets (with generated observations) were looked at carefully and the results compared. For this reason, even though not first planned, separate univariate tests were conducted on the individual time points, using both the original (with missing records) and the complete (generated) data sets, as a means of comparing methods only. This approach was also applied to the summary measures from the original and the complete data sets and these results were also compared. These methods were conducted on both data sets A and B. There were no vast differences between the results before and after data replacement. Due to the similarity of figures produced before and after data replacement, only those using the data set with missing records are displayed, to show the behaviour of the data across or over time.

In analysing both data sets A and B, it was decided to analyse the data using multivariate testing and mixed modelling techniques, since this is one of the most efficient methods of dealing with repeated measures data. Of the various SAS procedures of conducting multivariate-modelling techniques, there are two commonly used procedures in dealing with modelling continuous data. These are Proc GLM and the more recent method of Proc MIXED. Details on these and other SAS procedures used in the analysis of the data for this thesis are described in section 2.6.

After gaining a general feel for the topic, it was found that when most multivariate repeated measures data analysis are conducted, various assumptions (including normality, equal correlation between groups and equality of variance) need to be made about the distribution of the data for the tests to be valid. Even though computing resources allow computation methods, which previously were not possible for

multivariate analysis of variance, there are still occasions that problems can occur with multivariate analysis of variance (MANOVA). A specific case is when there are more repeated measurements than the number of individuals within a group [27, 35] and hence normality of the data may not be a reasonable assumption. This happens to be the case for both data sets A and B.

The main purpose of our research is to see what happens if the usual assumptions of normality is not met. Some methods from the literature, that are used to analyse this form of data, when these general assumptions are not valid, are looked at and finally some alternative ideas are suggested to those used in practice. A suggestion to overcome this problem as mentioned in the literature, was 'Response Features Analysis' or the 'Summary Measures' (S.M.) approach [24,43]. The approach was for one single summary measure to represent the whole profile for an individual. This summary measure would then be analysed using some univariate testing method such as the parametric analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test (for comparing more than two treatments). Chapter 5 describes the results obtained from analysing the data using this S.M. approach. The disadvantage is that multivariate methodology gets lost in using this procedure.

The approach of dealing with multivariate data with the problem of having more measurements than individual profiles has not been greatly focused on in the literature. For this thesis, it is suggested that the best method of dealing with the data, so a robust multivariate analyses could still be conducted, was a segmentation of the data with data reduction of some kind. Chapter 6 gives details on suggested approaches for data reduction in order for a valid multivariate approach to be applied. Three methods of data reduction were looked into. One of the methods was an extension of the S.M approach using a set of 6 summary measures (mean, median, min, max, q1 and q3) together to describe each individual profile. These data were then analysed in a multivariate rather than univariate fashion. The second approach, was an extension of the idea mentioned by Jones and Rice [33] who used P.C.A to reduce the number of individual profiles. The approach used in this thesis reduced the number of time points instead of the number of individual profiles. The final approach, which was suggested for the purpose of this thesis, was to use the mean of every two (for data set A only) or three (for both data sets A and B) observations instead of each time. This method yields a data set that still preserves a time element whereas the other two methods do not maintain this factor. Multivariate tests were conducted to see whether the three approaches give similar results or whether one approach is better than another. All multivariate test approaches were conducted on the data before and after data replacement to see if similar results were

obtained whichever method was applied and whether missing data would be an issue for multivariate testing. The multivariate method of Mahalanobis distances was used to test for treatment differences for all the above mentioned data sets. The results from each of the multivariate tests were then compared and these are shown in chapter 7. Multivariate testing was affected by missing data since records were not retained during analysis.

All multivariate mixed modelling procedures were conducted on both the original data before imputing missing records and also on the reduced data obtained from the complete data set (after data generation) to maintain consistency with the multivariate tests that were previously conducted. It was, however, not necessary to work with a complete data set since Proc MIXED is not affected by missing data. The procedure was applied to only the reduced data, using the reducing procedure of averaging over segments of time, since this was the only reduction approach that retained the element of time as with the original data. This allowed a comparison of results before and after data reduction. Chapter 8 shows the findings of the mixed modelling approach. Each of the variables after being reduced by averaging in groups of three measurements (or two measurements if possible) were modelled using a mixed modelling approach after adjusting for baseline reading and time. Individuals were modelled as random effects in the models. No conclusions could be drawn about any other reduction methods since time was lost in the calculations.

From conclusions described in chapter 9, it was found that the data before and after imputing missing information gave similar findings. The best data reduction approach appeared to be the summary measures (SM) approach for testing the data and also the grouped mean (method 1) for modelling the data. Details of further work are also discussed in this chapter.

In conducting the initial exploratory analysis, there were some problems and issues that were encountered. Some of the main issues that led to problems during the analysis of this data set were missing observations and imbalance between treatment groups. Missing data was not an issue when it came to analysing data in a univariate manner. The problem occurred while conducting any multivariate methods (P.C.A. and Mahalanobis Distance) on the data set with missing information, especially if there were many individuals with missing data. One of the most up to date approaches of modelling such data is using Proc MIXED, since these issues do not tend to be of concern using this technique.

CHAPTER 1: Repeated Measures Data Structures and Collection

1.0 Introduction

The subject of 'Repeated Measures Data Design and Analysis' is a very broad research area. Wishart (1938) [62] and Greenhouse and Geisser (1959) [27] conducted some of the earliest research in this field. It is only in the recent years (since 1980) that the area has become very popular and the field is still growing to this date. Among the various books published in the area, Crowder and Hand [14,30], Diggle, Liang and Zeger [18] and Vonesh and Chinchilli [61] are among the most popular and up-to-date ones. All of these books were published in the late 1980's to mid 1990's. These books and references therein will give the reader a broader insight into the topic of research and may enlighten as to the variety of both the old and new literature available and the various works that have been conducted in this field. There have been a variety of works published in the area of 'Repeated Measures Data'. There is still, however, a large potential for other research ideas in the spectrum of research readily available.

Repeated measures data can arise through various experimental designs including spilt-plots, cross-over trials and parallel groups design experiments but to name a few [36]. For the purpose of this thesis, only repeated measures data from a longitudinal setting will be focused on. The terms 'Longitudinal Data' or 'Repeated Measures Data' will be used interchangeably to refer to the data used during analysis.

The present chapter introduces the reader to repeated measures data structures and collection. The structure of specifically a longitudinal data set in both an ideal and a messy situation are described in section 1.1. Some of the shortcomings of repeated measures data, as described in section 1.2, include the problems of missing data, unscheduled visits, non-balanced data, early dropouts and unequal spacing between visits. Another issue, which is to be the main area of focus for this thesis, is when the repeated measures are large compared to the number of individuals on whom they are measured [27,35]. Ideas are suggested on how to control some of these problems but it must be noted that some of these suggestions may not sometimes be applicable. Section 1.3 gives details and examples of study designs used to obtain repeated measure data. Section 1.4 explains the main reasons for collecting this type of data and mentions some questions that may be asked during the data analysis stage. An overview of this chapter is given in section 1.5.

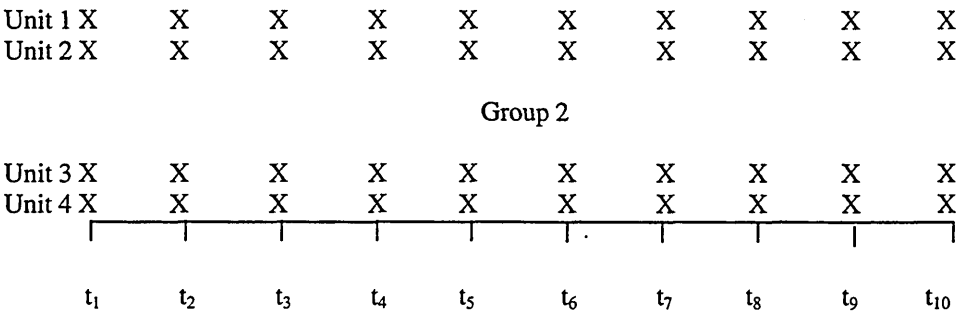
1.1 Repeated Measures Data Structures

This chapter is intended to give the reader an introduction to repeated measures data structures. Below is a description of what repeated measures data actually are and how these types of data are obtained. Repeated measures data are multiple recordings of an observational unit or the same dependent variable, (e.g. blood pressure, heart rates or some other measurement), which are taken for each of a number of individual experimental or primary sampling units (e.g. patients, subjects or some other individuals). The experimental units are randomly selected to represent various strata or are randomly assigned to levels of a grouping factor (e.g. therapy, treatment or some other group). In other words, an individual can either be allocated to one of several groups or can fall into one of a number of naturally occurring groups. The responses that are being measured under the various conditions are the observational units and these can be taken (or measured) at various points in space or time. In our research, we will be looking at biomedical data. However, repeated measures data can also arise in a wide variety of other contexts or research areas such as agricultural, psychological, economic and social research.

Initially an important thing to remember is that 'Repeated Measures' are the type of data, not the design of experiment, which is a mistake that is often made. The terminology that is often used to explain the set of multivariate repeated measures data for an individual unit is an individuals profile. This can be seen more clearly in the diagram below which shows data collected in a longitudinal manner in an ideal situation.

Example 1: An Ideal Situation:

REPEATED READINGS OF THE SAME RESPONSE VARIABLE



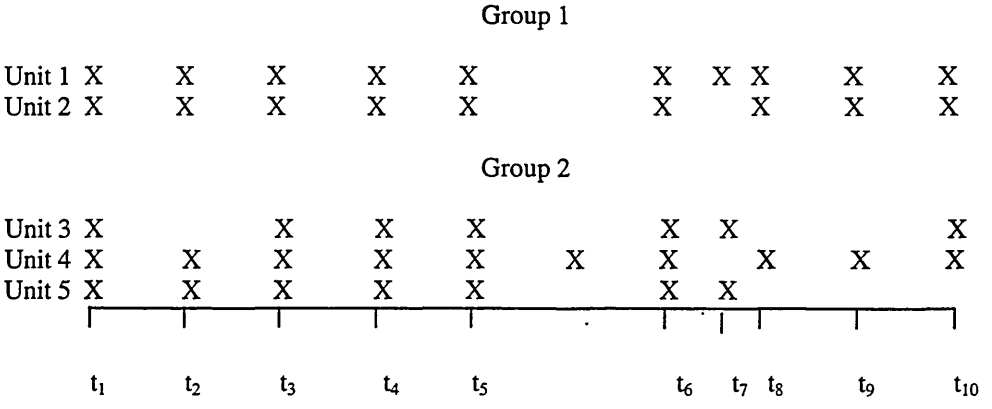
Times of Readings (Days)

Here, is a simple example where there are four individuals each randomly allocated to one of two groups 1 and 2 (i=1, 2). Hence, each group includes two individuals (j=1, 2) and ten readings are measured on

each of these individuals at the *same time points* (k=1 to 10). The ten time points are *equally spaced* apart. There are *no missing data* in this example and the *data are balanced* between groups. Hence this is repeated measures data from a 'balanced complete longitudinal' design. The general notation for any individual observation using the information from above would be Y_{ijk}. So, for example, the individual observation unit 3 at time 3 from group 2 would be shown by Y_{213}.

Note: As can be seen in the example above, in an ideal world it would be preferable for each sampling unit to have measurements at the same times and also for there to be equal spacing between each pair of response measurements or readings. Another thing that is preferable is the complete collection of data. However it is not always possible in most real situations for us to meet all the criteria mentioned above while collecting data and there usually tends to be a shortcoming in at least one of the conditions mentioned above. The diagram below shows some of these shortcomings in a clearer fashion for longitudinal data collected in a messy situation.

Example 2: A Messy Situation



Times of Readings (Days)

1.2 Problems With Data Structures

Data structure problems can lead to problems during analysis. Some of these problems are mentioned below and are illustrated in Example 2 above:

a) Unequally spaced time points between measurements.

In the situation above, the design is such that the data measurement is not at equally spaced time points. The main reason for this could be due to the fact that measurements can only be taken at certain times because of external or environmental factors. An example would be if it were known, before the study began, that there were specific times that the outcomes of interest would occur and these would be the time points where special attention would be given. The problem of unequally spaced time points can

also occur in a designed experiment with equally spaced time points when there are unscheduled visits. The main difference is that for the designed experiment the additional set of information could always be dropped for analysis purposes. However, if the study was set up to measure data at unscheduled visits this could not be done. It must be noted, however, that it is not always practical to set up an experimental design with equal spaced time points, especially if the variable being measured is only available at certain times. In this case, an appropriate method of analysing the data would be using a time series approach.

b) Unscheduled visits.

There is one extra reading for unit 4 that is measured at an unscheduled visit between t_5 and t_6. This would mainly be due to the availability of the sampling unit. For example, a patient knows that he or she can not make their next appointment and therefore turns up early to tell the doctor of the situation. The doctor still takes measurements in the hope that the data can be used. Even though it is not planned, it is sometimes believed that partial data is better than no data at all. If the study were a designed experiment with equal spacing between measurements, there would be justification in removing any additional data especially when they were unscheduled measurements. For a design that has unequal spacing between measurements the process of removing additional data would not be justifiable. This data should then be analysed as a data series again using time series techniques.

c) Incomplete / Missing data at scheduled visits.

Sampling units 2, 3 and 4 all have missing readings that were supposed to be measured at scheduled visits. The main reasons for this could be that the equipment being used to measure the data fails or that the sampling unit might not be able to make the scheduled appointment. Both a designed experiment or a study that is not designed could yield missing data and it is believed that this is something that can not readily be controlled whatever the design is. Having one missing record for a patient would force the whole observation to be dropped when most multivariate methods are applied to the data. This means that a lot of useful data is wasted. The solution in this case is to generate these missing data in some way, if possible.

d) Unbalanced data between groups.

It can be seen that group 2 has one more patient than group 1. This is an issue that causes problems in some analyses. The main way that this problem can be solved is by conducting a designed experiment. However, it must be noted that this problem can not be eliminated in all designed experiments since

there are times that patients drop out of a study directly after randomisation and hence there are different numbers of observations in each treatment group. It is believed that a designed experiment may have greater control over this issue than any other type of study. Depending on the size of the study and the numbers of patients within different groups, it is suggested that the data set could be made to balance by randomly dropping the extra data. Note that, this suggestion is only deemed to be appropriate if the data set is large enough as the loss of a small number of observations is not expected to affect the results greatly. For example, if there were either 21 or 22 individuals in each of 4 treatment groups and if the data set was forcibly balanced, for both treatment groups and centre, then one would end up with 20 individuals in each treatment group.

e) Early Termination

As for unit 5, a patient can drop out of the study before the scheduled time of completion. This means that the sampling unit does not have a full set of records. This is an issue that can not be controlled based on the design of the study. These observations would generally be dropped from any usual multivariate analysis on the data.

Another problem, which is to be a part of the main focus for this research, is as follows:

f) Number of Individuals are less than the Number of R.M.

When the number of repeated measures is greater than the number of individuals then there are problems in calculating the sums of squares (SS) and degrees of freedom (df) while conducting multivariate ANOVA [27]. When p is large compared to the number of residual df, a singular variance-covariance matrix is estimated and this in turn means that the MANOVA test statistic can not be defined [35].

A practical argument for explicit modelling of the covariance structure, as was stated by Diggle, Liang and Zeger [18] concerns the number (p) of repeated measurements per experimental unit. It was observed that when p is large, the objection to estimating $p(p+1)/2$ parameters in the covariance structure gains force since this expression is of the order of p^2. In extreme cases, p can also exceed the available replications.

A different problem also arises if the number of individuals is not considerably greater than the number of repeated measures. In this case, in most situations, the assumption of normality or having tests as in the case of normal distributions would not be reasonably valid. Hence a suggestion would be to reduce the number of repeated measurements in some intuitive manner in order to have the validity of the model with desired properties [see 2.1.1 and 2.1.2]. This provides more robust statistical tests. At this stage, a

reasonable question may be: 'Would all of the many repeated measures be of relevance or could a fewer number of measurements give the same results as all observations?'

1.3 Obtaining Repeated Measures Data

1.3.1: Data Collection

Generally, most data sets are obtained by one of the following three methods [40]. All three types of data collection mentioned are very different but they all use very similar statistical notation in that they all have 'factor', 'level' and 'effect':

A) Designed Experiments

As the name suggests, a designed experiment is planned or designed before the study takes place.

Example:

> ***Experimental units (patients) are randomly assigned to one of four groups (drugs 1-4). After the experimental units are assigned to their groups, responses (heart rates) are measured.***

For this designed experiment, therapy would be a 'factor', and each drug would be a 'level' within the factor. Each level would have an 'effect' on heart rate. So applying any one of the drugs has an effect on the heart rate of the patient.

B) Sample Surveys

A survey design is a plan that is used to collect data on the sampling units but treatments are not applied to these units. The sampling units are usually people and they already have certain pre-existing attributes e.g. age or qualifications. The data to be measured could be a variable such as salary and this can be determined for each individual sampling unit.

Example:

> ***A survey could be taken on a set of individuals to see how individual salaries behave based on qualifications.***

For this survey, qualifications would be the 'factor', and each 'level' (A, B) of the factor would have an 'effect' on salary. Note, a particular qualification would not cause the level of the salary but people with qualification A may tend to have a larger or lower salary than people with qualification B.

C) Observational Studies

The sampling units here already exist before data is collected and they are not from a planned study.

Example:

> ***Patients visiting a doctor's office at the time of visit have their weights measured and they are categorised into groups based on this information. The blood is then tested for levels of cholesterol.***

For this observational study, weight would be the 'factor' and each weight measurement would be a 'level' of the factor. Differences in the cholesterol level between the diagnostic groups would be 'effects' of the factor levels.

1.3.1.1 Choice of Data Collection Method: In General.

A question now is 'which type of design should be used in general?' It is usual for the experimenter to go with the most convenient method of data collection based on certain external factors that can not be controlled. The person conducting the study should decide based on the following factors before they begin data collection:

1. The aim of the project.

   A survey could be looking into specifically a small population, such as of an ethnic origin, since it is of interest. This, in turn, could lead to a smaller sample size than one would actually prefer and so could lead to problems with data analysis. If the study is observational in nature, then the investigator has no choice than to go with what is available. A designed experiment is usually the best way of controlling the data obtained.

2. The cost of the project.

   If fewer financial resources are available than are required, this could again influence the amount of data collected. A designed experiment is often more expensive to run than an observational study or a survey.

The points mentioned here may be obvious but can often get overlooked. The aim would be to set up a design, which captures exactly what the experimenter wants, before starting to collect the data. If the data can be obtained through a designed experiment, then this is recommended since it is believed that this would reduce some of the problems associated with data analysis after the data has been gathered.

1.3.1.2 Choice of Data Collection Method: For Repeated Measures Data.

Specifically with regards to longitudinal data, two important issues that lead to problems with data analysis are of missing data and early termination. Neither problem can be controlled by study design. Conducting a designed experiment or survey can usually control the problems of unequal spacing between time points and unscheduled visits. This is not true when the variable being measured is restricted to certain times of measurement, as in an observational study or a study of convenience, where there would be no solution to this problem. Unbalanced data can be controlled if a balanced study design is conducted with no dropouts.

Hence, it is suggested that the best way of obtaining repeated measures data, that in the end will be easier to analyse, is to obtain the data using a designed experiment or survey. A number of factors need to be taken into account when collecting data such as the aim, cost and efficiency. A designed experiment or survey does not control factors such as malfunction of a machine used to measure the variable of interest, early termination from the study or other environmental factors. It should be noted that once it is decided to obtain the repeated measurements for a particular variable then the data design usually ends up falling into the category of a 'designed experiment'. This is the case whichever initial method was used to classify the observational units into experimental groups. There is usually some sort of planning in the process of collecting repeated measures data. It should be noted that the data sets that are to be used for this thesis are from designed experiments.

There are various standard designs for experiments that fall into the category of a "designed experiment" and a detailed explanation of these can be found in various texts. Due to time constraints, further details of designed experiments will not be given in this thesis. The reader can refer to any books with 'Experimental Designs' or 'Designed Experiments' in the title and any references therein [12, 44,64]. Further details are given below on the designs used to obtain repeated measures data in particular.

1.3.2: Designs Used to Obtain Repeated Measures Data

Many different designs can be used to obtain repeated measures data. Experimentation and collection of repeated measures data are very important since the collection of such data particularly allow comparisons of treatment effects over time. There are a wide variety of study designs that can lead to the collection of repeated measures information. Of these, the four most important study designs are longitudinal, source of variability, crossover, and split-plot studies. A combination of any two or more of these methods can also give us repeated measures data. For all study designs mentioned, every

individual unit is observed under two or more conditions. Koch [36] gives a good overview together with references for all four designs with some examples of each and also some statistical methods and applications particularly in reference to split-plot designs. The advantages and disadvantages of each design and similarities and differences between them are also mentioned.

We will begin by giving a brief example of each of the four designs with a brief overview of similarities between the design structures and any important points of discussion. The main body of the report will, however, focus on repeated measures from a longitudinal study, and the analysis of such data.

A) Split-Plot Experiments:

Example:

> ***Sixty-four laboratory rats are randomly divided into four groups of 16. Each group of 16 is assigned to a block of 4 cages (with 4 rats in each cage). Four dietary calcium sources are randomly assigned to the four cages within each block. Four rats are assigned to each cage. Four implants (A, B, C ,D) are randomly assigned. [Littell [70]].***

Split-plot designs have differences compared with other designs in that they have more than just one stage of randomisation. Subjects are initially randomly assigned to treatment groups or selected from strata. Conditions are then randomly allocated within these groups or strata.

Treatment groups can be based on a single factor or on a cross-classification of two or more factors. They can be assigned to whole plots based on a completely randomised, a randomised complete blocks or a type of incomplete blocks design. Conditions can similarly be assigned to split-plots.

These designs are commonly used in agricultural experimentation, where the subjects are whole plots or fields within which split-plots are the observational units.

B) Cross-Over (or Change-Over) Designs:

Example:

> ***Each subject is randomly assigned to either sequence AB or sequence BA. Responses to each successive treatment are measured for an allocated period. The conditions are the time periods and treatment and also the proceeding treatment.***

The subjects within a crossover design are randomly assigned to treatment groups or are selected from strata. They are randomly assigned with alternate treatment sequences. One could seek here estimation of time, location or treatment effects etc.

For a cross over study, the previous treatment can influence the response on a particular treatment and so a carry over or residual effect may occur. If it is known that the extent of carry over is more than negligible then some sort of adjustment is needed. It has been suggested that sequences should be devised to allow estimation of location, treatment and carry-over effects. This at times can be hard to implement. An alternative design where each subject gets only one treatment eliminates this problem.

C) Source of Variability Studies

These studies identify the amount of variability between responses attributed to each component of the sampling process or measurement process.

Example:

> ***The assessment of variability associated with clusters of households and interviewers. This is to be done in a survey of socio-economic variables. A random sample of 288 clusters of 8 households is randomly divided into 3 sets (A, B and C) of 96 clusters. 24 interviewers are randomly assigned to each set of clusters. Each assignment in the protocol is made at random. In set A each interviewer is assigned 4 clusters and obtains responses from all 8 households within each cluster. Within group B, each of 12 pairs of 2 interviewers is assigned to 8 clusters. Each pair of interviewers is then assigned 4 households from each cluster. For group C, 6 blocks of 4 interviewers are formed. Each block is assigned 16 clusters. Each interviewer within the group of 4 is then assigned 2 households from each of the 16 clusters*** [36].

Studies of source of variability can deal with fixed and random components of measurements. Their structure varies and can be anything from very straightforward to very complex.

D) Longitudinal Studies:

For longitudinal studies, the observational units for subjects are associated, rather than assigned randomly, with the conditions. The association is usually through space or time. Longitudinal study designs are specifically parallel groups of subjects, which can be either randomly assigned to treatments or randomly selected from strata or both.

Example:

> ***A much-cited example in the literature is of the experiment on the control of intestinal parasites in cattle. Cattle ingest roundworm larvae during the grazing season (from spring to autumn). The larvae have developed from eggs previously deposited on the pasture in the***

faeces of infected cattle. Once an animal is infected it is deprived of nutrients and its immunity to other diseases is lowered. This then can greatly affect the cattle's growth. In order to monitor the effect of a treatment on the disease, the observations need to be measured through out the grazing season. In an experiment to compare two methods A and B for controlling the disease, 60 animals were randomly assigned to two treatment groups each of size 30. The animals were put out to pasture at the beginning of the grazing season and the members of each group received one of the two treatments. The weight of each animal was recorded 11 times to the nearest kg. The first 10 observations were made at biweekly intervals and the last measurement was made at a weekly interval. [Kenward [35]].

The cattle are the subjects and the successive time intervals are the observational conditions. The experimental unit being measured is weight. Many designs can be classed as being longitudinal in nature and, as already mentioned above, this thesis focuses mainly on this type of design.

1.3.2.1 Discussion of Designs Used to Obtain Repeated Measurements

For longitudinal, split-plot and crossover designs, the subjects are randomly assigned to or are selected from strata. Both longitudinal and crossover trials have similar concepts since individual subject responses are measured at many points. Split-plot studies are slightly different since the researcher has a control over the variability of influencing factors between conditions by controlling the whole plot units. Designs can be conducted to control carry-over effects, but designing a study can be complicated and expensive. Since both split-plot and crossover designs have conditions assigned to periods, they both have similar pros and cons.

Advantages here are:

1) Designs require fewer subjects so costs can be reduced. They are also simple to conduct.
2) Comparisons between within subject treatment conditions and interaction effects can be accurately estimated.

Disadvantages are:

1) If carry over effect is not accounted for the results can be biased.
2) Greater cost or effort is required for the administration of split plots experiments to ensure each condition only affects the split-plot to which it was assigned.

An important part in the analysis of longitudinal studies concerns the amount of data being gathered (e.g. the time intervals). Increasing the amount of data can increase the information. However, the cost and

effort of gathering more information also increases if not collected and processed automatically. The selected design usually leads to the required information based on resources. Take caution, however, that obtaining too many time points of data can later lead to problems at the time of data analysis [27, 35].

1.4 Aims of Any Repeated Measures Data Collection and Analysis

The general aim of collecting any repeated measures data is to get an idea of how each variable being measured is behaving 'as a whole' over space (or time). The method of conducting repeated measures analysis varies among researchers and it is generally proposed that this could be done in either a univariate or multivariate fashion depending on the assumptions being made just prior to the time of analysis. Generally, during any analysis there are always some initial questions that need to be asked regarding the data set being looked into. Examples of some relevant questions would be:

1. Do some patients have specifically more abnormal readings than others?
2. Are there any differences between the distributions of treatment groups over time? If so, when do these differences occur?
3. Are there any vast changes from baseline (pre-treatment records)?

The purpose of the analysis would be to answer the most appropriate questions asked in the most feasible manner.

1.5 Overview

Repeated measures data are the type of data not the design of study. Various study designs can be used to obtain repeated measures data including longitudinal, crossover and split-plot experiments[36]. Longitudinal data analysis is only a small sub-section of the larger general topic of repeated measures data analysis. However, for the purpose of this thesis, any further mention of repeated measures data analysis will be in reference to longitudinal data sets only.

The next chapter will focus on some of the statistical methods that are commonly used to analyse longitudinal data sets. In the past, computer packages were unavailable to analyse large longitudinal data sets and hence simpler methods were selected to analyse such data. Nowadays, with the advance of computers and the availability of statistical software such as SAS, computational analysis is not quite so difficult and so more complicated mixed modelling methods are used. Some of the old and new approaches of analysis are touched upon if considered appropriate, even though they are not used to analyse the observed data sets for this thesis. Some general requirements/assumptions for analysis purposes are also addressed.

CHAPTER 2: Data Analysis and Assumptions

2.0 Introduction

The aim of the present chapter is to give some background into some of the analysis methods that are commonly used to analyse a set of continuous multivariate observations in time or a longitudinal data set. We will review as much of the available literature as possible and summarise this information in an appropriate manner.

Categorical data methods for repeated measures data is a topic in its own right and there are various publications in this area. This is not of concern for the primary analysis, hence, we will not be going into the details of any of the categorical data approaches. We will only touch on some categorical data methods if considered appropriate. See Stokes et al [57] for a list of references related to categorical data analysis methods only.

If a longitudinal data set is created via multiple measurements of a particular variable in time, the data set could have a layout containing:

(1) A baseline measurement (pre-study) of the variable and various measurements thereafter.

(2) All observations could occur on-study.

(3) Other variables (covariates) could also be measured and there could be either varying as within-unit factors or between-unit factors.

(4) There could be either one study group or many study groups being tested.

The concept, which will be used here in considering a longitudinal design study, is that each individual is assigned to only one study group. There are various methods of analysing such data. The data can initially be analysed in a univariate format by testing the behaviour at each time point individually or in a multivariate format by testing the behaviour at all time points together. The initial thing is to decide the purpose of the analysis:

(1) To test for general group differences.

(2) To test for profile differences.

(3) To model the data using either a linear/non-linear approach.

The aim of the analysis of our data would be to look for study group differences based on external factors. Some useful SAS commands will be given in this section.

2.1 Assumptions about the Distribution of the Data.

2.1.1: General Assumptions

All statistical methods of analysis have some underlying theory regarding the F distribution. Some underlying assumptions need to be met in order for the F distribution and, hence, the F-test to be valid. The most important of these are the assumptions of:

a) Normality.

b) Homogeneity (or equality of variance between groups).

c) Mutual independence or more generally equal correlation's between groups.

Note that in practice it is not always possible for all three of these conditions to be met precisely. Even when these conditions, or when assumptions of asymptotic tests relative to these models, are met approximately, one could still draw reasonable conclusions via F-tests. Parametric approaches require an assumption of the underlying distribution of the data such as normality. Estimation and testing are based on the assumptions that are made about the distribution of the data. Non-parametric methods do not make such distributional assumptions about the data. The main advantages of non-parametric methods are that inferences tend to be general and the methods can be used when the distribution is unknown or the parametric assumptions are invalid. The main disadvantages on the other hand, are that the approaches are less powerful than parametric ones when the assumptions are not met. However, most of the time, the loss in power is not large enough to make much of a difference. The most powerful non-parametric approach is the Manzel-Haenzel approach, which can generally be used in place of most other non-parametric methods [58].

2.1.2: Normality

The most stringent condition that is required for any parametric approaches is that of normality. If it is known that the data are not normal in nature (if the data is skewed), then a log or some other transform of the data is usually recommended before carrying out any further parametric analyses [7, 8]. Paik [47] suggested using a parametric variance estimation approach for non-normal repeated measures data. Univariate normality is easy to test for using Proc Univariate in SAS with the NORMAL option. Here, the following hypothesis is usually tested:

H_0: The data is normal.

Multivariate normality is not as straightforward to test for. Usual methods to test for multivariate normality would be to conduct a regression analysis and to analyse the residuals and hence make

assumptions about the distribution of the data based on the distribution of the residuals. Some researchers assume multivariate normality without testing and specify conditions for the variance-covariance matrix. If after transformations, normality is still not achieved, then one could explore the possibility of using a non-parametric approach to analyse the data. In the case where j (the number of individuals) is much larger than p (the number of repeated measures) then the approach of assuming asymptotic normality can be taken, as the asymptotic tests in that case behave essentially as in the case of normal populations. Initially we will provide an example of a bivariate non-normal distribution with normal marginals and zero correlation. This is done using a general construction.

Initially, we consider two independent random variables X and Y having the probability density functions f (x), $x \varepsilon (-\infty,\infty)$ and g (y), $y \varepsilon (-\infty,\infty)$ respectively. Here the marginal densities are assumed to satisfy the following condition:

$f(x),g(y) \geq \alpha > 0$, where α is a positive constant and x and y are points in the interval (a,b). **[1]**

Due to there being independence, the bivariate joint density of X,Y is the product of the marginals. Hence, it is given by $f(x)g(y)$, $x \varepsilon (-\infty,\infty)$, $y \varepsilon (-\infty,\infty)$.

A second situation is to consider two uncorrelated dependent random variables X* and Y* with a bivariate joint density function h(x,y) defined clearly below:

FIGURE A: Constructing Uncorrelated Dependent RV's With Marginals as Required

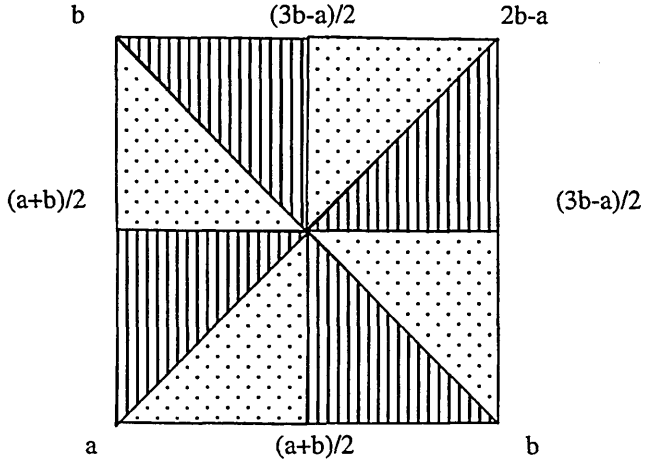


FIGURE B:

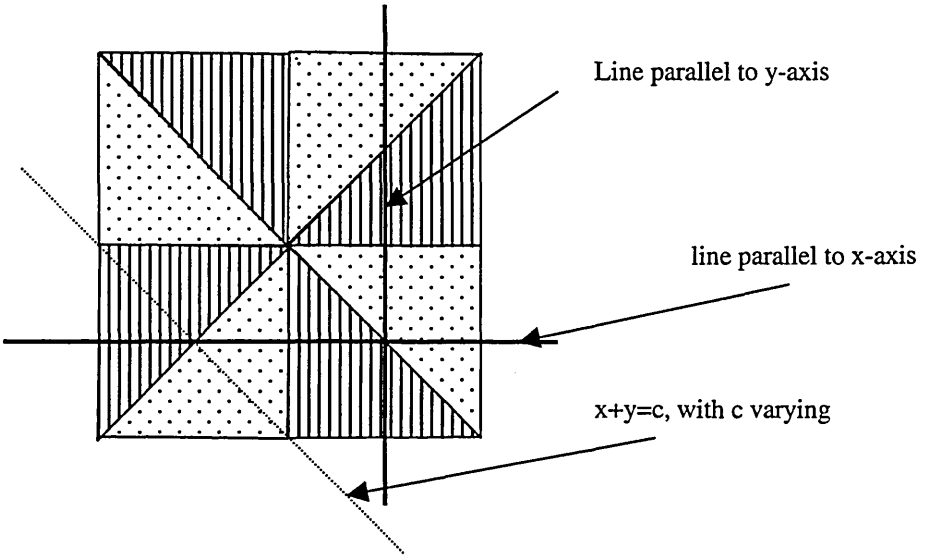


Figure B above, shows the construction described in Figure A after adding three lines.

We define here:

$$h(x,y)=\begin{cases} f(x)g(y)+\alpha & \text{if } (x,y) \text{ is the area shown by dots} \\ f(x)g(y)-\alpha & \text{if } (x,y) \text{ is the area shown by lines} \\ f(x)g(y) & \text{if } (x,y) \text{ is elsewhere.} \end{cases}$$

It can be seen from the symmetry in the picture in Figure B above, that the deviations (α) from the density values f(x)g(y) corresponding to (X,Y) on the lines shown cancel out. Hence, the marginal densities of X*,Y* and X*+Y* are the same as those of X, Y and X +Y respectively.

If the bivariate vector (X*,Y*) is taken to be a random vector with density h(x,y)

and the bivariate vector (X,Y) is taken to be a random vector with density f(x)g(y)

as described above, then it follows from all the information above that:

a) X* is distributed as X,

b) Y* is distributed as Y

c) X*+Y* is distributed as X+Y.

Since X*, Y* and X*+Y* have the same distribution as X, Y and X+Y respectively, the corresponding moments are also the same. We will now consider only the second moments.

If X and Y have the distribution such that $E(X^2) < \infty$ and $E(Y^2) < \infty$, then

$$E((X^* + Y^*))^2 = E(X^{*2})+2E(X^*Y^*)+E(Y^{*2}) \qquad \textbf{[2a]}$$

$$E((X+Y)^2) = E(X^2) + 2E(XY) + E(Y^2) \qquad \textbf{[2b]}$$

$$\text{and } E(X^{*r}) = E(X^r), \qquad \textbf{[3a]}$$

$$E(Y^{*r}) = E(Y^r), \qquad r=1,2. \qquad \textbf{[3b]}$$

From [2a], [2b], [3a] and [3b], it follows that

$E(XY) = E(X^*Y^*)$

Since

$cov(X,Y) = E(XY) - E(X)E(Y)$

$= E(X^*Y^*) - E(X^*)\,E(Y^*) = cov(X^*,Y^*)$ **[4]**

and X and Y are independent implying Cov(X,Y)=0, the covariance between X* and Y* equals zero and X* and Y* are therefore uncorrelated.

However, from the construction, it follows that the joint density of X* and Y* does not correspond to that of independent R.V.'s , implying that they are dependent R.V's. This is because the marginal densities of X* and Y* are f(x) and g(y) respectively and there are some areas in Figure A where $h(x,y) \neq f(x)g(y)$.

By taking f(x) and g(y) to be normal, we can produce a bivariate distribution for which the random variables are uncorrelated but dependent. This also implies that even though the marginals here are normal, the bivariate distribution is not normal. For bivariate normal, uncorrelatedness implies independence. Since we have in our case R.V is that are uncorrelated but dependent, it follows that their joint distribution is not bivariate normal.

If we take $(X_1,\ldots X_p)$ with (X_1,X_2) distributed as (X^*,Y^*) and $(X_2,\ldots X_p)$ as normal and independent of (X_1,X_2), then we have a p-dimensional non normal random vector with normal marginals having zero correlations.

If we are not looking for the new random variables that are not uncorrelated, we get a slightly simpler construction of a bivariate distribution that is not normal, but has normal marginals; for an alternative construction of this, see below:

Consider the situation of independent random variables X and Y having probability density functions: f(x), $x \in (-\infty,\infty)$ and g(y), $y \in (-\infty,\infty)$ respectively.

Here the marginal densities are assumed to satisfy the conditions as before in [1].

Next consider two dependent random variables X* and Y* with the bivariate joint density function h(x,y). This is defined after Figure C and D:

FIGURE C: Constructing Dependent RV's With Marginals as Required

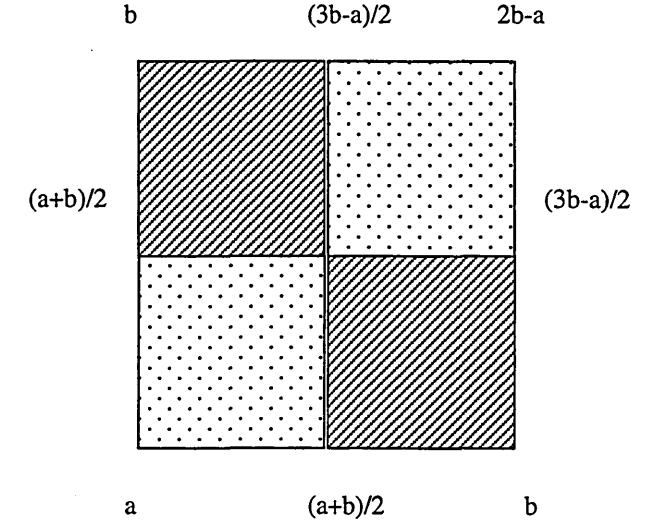
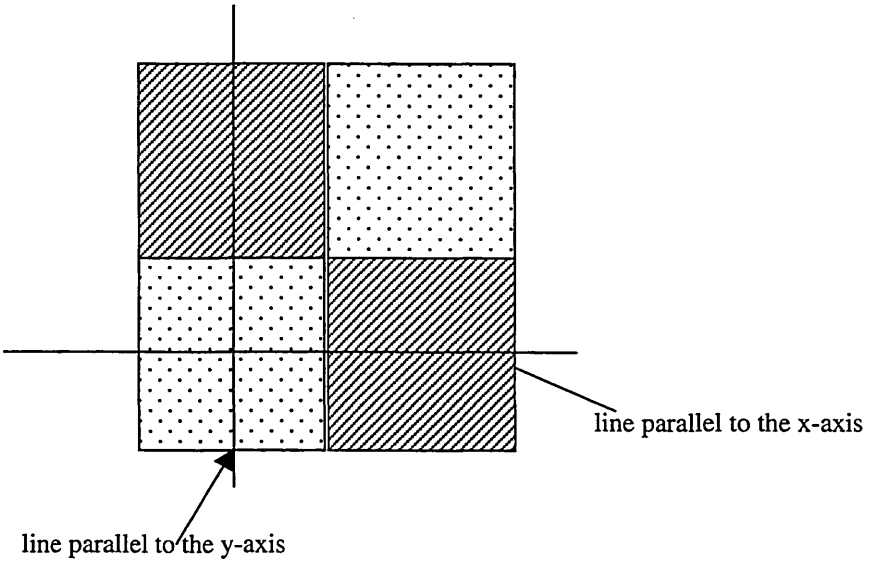


FIGURE D:



Define now h(x,y) such that:

$$h(x,y)=\begin{cases} f(x)g(y)+\alpha & \text{if } (x,y) \text{ is in the area shown by dots} \\ f(x)g(y)-\alpha & \text{if } (x,y) \text{ is in the area shown by lines} \\ f(x)g(y) & \text{elsewhere.} \end{cases}$$

We can now see that the marginal distributions of X* and Y* have densities f(x) and g(y) respectively. If we take f(x) and g(y) to be normal, then it follows that h is the density of a bivariate non-normal distribution with normal marginals. Also, now $(X_1,X_2,\ldots X_p)$ can be taken as a vector as defined before, but, with (X*,Y*) as in the present construction. Incidentally, the vector obtained from the previous construction has X_i's to be uncorrelated and marginally normal, and in the present construction we have X_i's to be just normal.

Note: following the insertion of the lines in Figure D the deviations from the densities relative to X and Y cancel out as was shown in the previous example.

From the above construction, it is clear that even when we get the respective samples at the various time points to be from a normal distribution, it does not follow collectively that the normal distribution assumption usually taken for "Repeated Measures Data Analysis" is met. A way of testing for multivariate normality would be the recommendation of some approximate techniques.

There is a characterisation of the multivariate normal distribution that a vector $(X_1,\ldots X_p)$ is multivariate normal if and only if every linear combination of $X_1\ldots.X_p$ are univariate normal [See Theorem 2.6.2 in Anderson (1958) [3a]]. Since any multivariate normal distribution is determined by the corresponding moments (i.e. by $E(X_1^{k1} \ldots.. X_p^{kp})$ with k1.....kp as non negative integers) it is possible to have a slightly improved version of the result just stated. The improved version is that a vector $(X_1,\ldots X_p)$ is multivariate normal if and only if $m_1^{-1}X_1+\ldots\ldots+ m_p^{-1}X_p$ is univariate normal for each positive integer m_i, i=1,2....P.

This is so especially because the moments are determined by $E\{\exp(\sum m_i' X_i)\}$.

Following this, one could suggest an appropriate technique to test normality as follows:

Choose a sufficiently large number N and test univariate normality of $m_1^{-1}X_1+\ldots\ldots m_p^{-1}X_p$ for integers $m_1,\ldots.m_p$ =1,2,.....N. If we have positive conclusions for most of the linear combinations, then it is reasonable to expect $(X_1,\ldots X_p)$ to be approximately normal.

To test for multivariate normality, one could also devise alternative techniques.

If $X_1,\ldots,X_n$ is a reasonably large sample from a population, then, provided $n \geq 3$ and $E|X_r| < \infty$, we have that $E(\sum X_j/n|(X_1 - \sum X_j/n))$=constant. [5]

If and only if X_r's are normal [see Kagan, Linnik and Rao[34] for the result by Ramachandran and Rao].

The result is also valid in the case when X_r's are vectors, and hence one could use this property to test for MVN. The test could be devised as follows:

Divide the sample on the p-component vector into smaller samples of equal sizes. Denote $\sum X_j/n$ and $X_1 - \sum X_j/n$ corresponding to these smaller samples (of sizes ≥ 3) by U_{1i} and U_{2i} respectively. Hence, the MV normality of $X_1, \ldots X_n$ can be seen to be equivalent to:

$E(U_{1i}|U_{2i})$=constant.

Thus, the problem reduces to that of testing a linear regression. To solve the problem, one could take the number of sub samples to be as large as possible to have the test to be approximately valid.

Incidentally, to go from the Ramchandran and Rao (R-R) characterization of the normal distribution in the univariate case to that for the M.V. case, we can use the characterization given in Theorem 2.6.2 of Anderson [3a] concerning M.V. normality referred to earlier.

Test in this case only the equations that the conditional expectations of the linear combinations of the components of U_{1i} with coefficients m_i^{-1}, given linear combinations of the components of U_{2i} with coefficients n_i^{-1} (where m_i and n_i are positive integers).

An adhoc approach for analysing the Repeated Measures data is to assume that different units are independent and that within each treatment group have an identical distribution. With appropriate changes to the data sets, one could apply the asymptotic theory relative to parametric tests such as Hotelling's T^2, Mahalanobis D^2 or likelihood ratio tests to test hypothesis relative to mean vectors or appropriate non-parametric tests for the hypothesies that various treatment groups have the same distribution. The tests applied are obviously more robust, when n is large.

Suppose the sample sizes n_1 and n_2 are large and the Hotelling T^2 is given by:

$$T^2 = \frac{n_1 n_2}{n_1 + n_2} (\bar{x}^{(1)} - \bar{x}^{(2)})' S^{-1} (\bar{x}^{(1)} - \bar{x}^{(2)})$$

(with obvious notational alterations) as mentioned on page 109 in Anderson [3a]. Then even when the two populations are not normal, under the hypothesis that the mean vectors of the two populations are equal, we have the distribution of T^2 to be approximately the same as that of $Y' \Sigma^{-1} Y$ where $Y \sim N(0, \Sigma)$. Here the Central Limit Theorem (CL) is being assumed together with the assumption of the populations having the same covariance matrix.

This follows because asymptotically, $S \approx \Sigma$, and under H_0,

$$\sqrt{\frac{n_1 n_2}{n_1 + n_2}} (\bar{x}^{(1)} - \bar{x}^{(2)})$$

is distributed as Y, where Y is as defined here.

From a well known result on quadratic forms it follows that the distribution of $Y' \Sigma^{-1} Y$ is χ^2 with p df. (Theorem 3.3.3 on p54 of Anderson [3a]). Thus even when the two populations are not assumed to be normal, the null distribution of T^2 becomes a approximately χ_p^2. Incidentally, Hotelling's T^2 is a constant multiple of Mahalanobi's D^2, which is given by:

$$D^2 = (\bar{x}^{(1)} - \bar{x}^{(2)})' S^{-1} (\bar{x}^{(1)} - \bar{x}^{(2)}).$$

For a normal model under H_0,

$$\frac{n_1+n_2-p-1}{p(n_1+n_2-2)}T^2 \sim F(p, n_1+n_2-p-1).$$

Indeed in view of the C.L Theorem, it follows that the tests used are asymptotically the same as those relative to the normal distributions as long as p (the number of components of the vector) is small compared to n_1 and n_2, or more generally $n_1 + n_2$. (Note that T^2, that is a constant multiple of D^2, has its asymptotic null distributions to be χ_p^2). This remark also applies to the likelihood ratio test or non-parametric tests for testing that the mean vector relative to the treatment groups are the same as long as p and the number of groups is not large compared to sample sizes for the groups involved.

In particular, in the case of the vector of 6 components of summary statistics, we can reasonably assume p (i.e. 6) is small compared to the n_1, n_2=24 and use T^2 or D^2 as an approximate test statistic, giving approximately a Chi-squared test.

Incidentally, if the whole vector is normal, then the components of the vector are normal, though the converse of this result as shown by our constructions is not valid.

In our analysis, if we find that the normality assumption is not met at some time points then it follows that the multivariate normality assumption for the data may not be reasonable. One could then look for ways to make asymptotic (more robust) tests applicable to our data.

The idea is then to reduce the number of repeated measures to a much smaller number so as to satisfy the condition that the number of individuals is considerably larger than the number of repeated measures, making asymptotic tests applicable. Under this situation there is no loss of generality in assuming that the data sets for units are from individual normal distributions.

2.2 Methods of Analysis

2.2.1: Plotting the Data.

An initial approach in conducting any type of analysis is to carry out some kind of exploratory data analysis (E.D.A.). We can begin by graphically displaying the data at each time point as follows:

1. Individual profile plots can be displayed together on one plot.

This type of plot can often become very clustered especially if there are too many individuals in the study. The following two graphs eliminate this issue.

2. Box plots show distribution of the data at each time point.
3. The group means at each time point with standard errors can be displayed together on one plot.
4. The summary statistics such as mean, median, minimum and maximum at each time point can also be displayed over time.

All plots above display the individual repeated measurements of data separately.

Data can also be summarised for all time points together by following the approach of the 'Response Features Analysis' mentioned in 2.2.2. Here each individual will have a set of single variables that each represents all the data as a whole (e.g. mean, median, minimum etc.). This information can then be summarised graphically as follows.

5. The data can be plotted as a histogram.

Each observation could be categorised as abnormal/normal and these results could be totalled over the whole study for each patient.

6. A scatter plot of the number of abnormal findings for each patient could be displayed.

The relationship between time points is often of concern. This can be displayed graphically as follows:

7. Correlograms are a common way to visually display correlations between the various repeated measurements for the data.

2.2.2: Response Features Analysis.

A recent approach called 'Response Features Analysis' or 'Summary Measures (S.M.) Approach' is to summarise or characterise the profile data for an individual into one or may be more summary measurements. This approach is pretty easy compared to some of the other analysis methods, that are commonly used to deal with repeated measures data. The summary measure needs to be chosen prior to data analysis and also should be useful in answering the question for the purpose of the analysis. After finding the summary measure, the approach is to analyse this data using some univariate approaches to

find out whether there are any treatment differences. It is possible, however, that more than one measure is required to best describe or summarise individual characteristics. In this case, a multivariate analysis approach would be required. There are various summary measures that can be used and the choice very much depends on the purpose of the analysis conducted. Some authors have used this approach to analyse repeated measures data, claiming that it has advantages over most of the other suggested methods [19, 20]. Matthews et al [43] gave a list of potential summary measures that could be used to conduct a response profile analysis. Summary measures could be any 'on-treatment' summary such as an individual summary statistic (mean, median, min, max etc.) or any other measure incorporating the pre-treatment or baseline data as well as the 'on-treatment' information (e.g. change in mean from baseline). Possible disadvantages with this approach are its loss of error degrees of freedom and differences in numbers of observations used to calculate the summary measures as discussed by Hand and Crowder [30].

2.2.3: Profile Analysis

The analysis conducted on the data set of individual profiles (or multivariate observations in time) is known as a profile analysis. The main aim of any profile analysis is to test for differences in levels or shapes between the various group profiles [27,30] by looking for 'time effects' and 'group effects' and 'interaction effects' through multivariate methods of testing. Some common questions that are used to answer these issues are:

1) Are the profiles parallel in appearance (or do they have the same shape)? If not, then this would be an indication of an 'interaction by group and time'.
2) Are the profiles all flat (or do the k variables being measured have the same mean)? If not, then the indicating would be a 'time effect'.
3) Do the group mean profiles have the same level? If not, then this would indicate a 'group effect'.

The aim would be to initially test for an interaction and if none exist, then the individual covariates are analysed as individual effects. The data can be summarised via either linear or non-linear modelling.

2.2.4: Time Series Methods

If the number of repeated measurements are large or there are longitudinal measurements that are unequally spaced in time, then time series methods could provide alternative approaches [3b, 11]. Time series methods [9] are not considered in this thesis.

2.2.5: Survival Methods

If the data include follow-up studies for the time to an event such as death or a disease of interest then suggestions have been made that the data can be analysed using survival analysis techniques [59, 63]. An approach could be taken to analyse the time to incidence data using Kaplan-Meier estimates and plot the cumulative survival estimates using Proc LIFETEST in SAS. The Wilcoxon test is appropriate for testing if most events occur at the beginning of the time range of interest and the Log Rank test is useful for testing events that don't occur until later.

The Kaplan-Meier estimate is given by:

$$\hat{S}(t) = \prod_{i=1}^{k}\left(\frac{n_i - d_i}{n_i}\right)$$

where k takes values 1....p and n_i is the number of patients with no abnormal reading before t_i and d_i is the number of patients with first abnormal reading at t_i.

The equation above is the product of the estimated probabilities of surviving up to the time point t_I, when t lied in the interval t_k to t_{k+1}.

2.2.6: Handling Missing Data

When analysing any data, there is often the issue of missing data and while collecting repeated measures for a variable on an individual it is not unusual to find that there are some missing records. There are many techniques that have been devised in the literature to deal with missing data. Commonly used techniques for dealing with missing data for repeated measures data are the 'Last Value Carried Forward (LVCF)' and 'Group Means' methods. Various works have been conducted using mainly the LVCF method but there is a range of varying opinions as to the circumstances for using this particular approach. A recent computer package called 'SOLAS for missing data Analysis 1.0' has been developed to deal with analysing data with missing records. The package is windows based and deals with single imputation methods including 'LVCF', 'Group Means' and 'Hot Decking' as well as multiple imputation methods.

There is continuing discussion on the pros and cons of using these and other imputation of generating missing data. The most obvious criticism is that the data points are not real and give the investigator a false impression. It is very easy to impute missing observations but these methods can often become abused if not approached with consideration. The main things that require consideration are the size of the data set and the number of missing records.

Among the several techniques available in the literature on how to deal with and model missing data, some methods have been suggested on modelling missing data mechanisms as part of the model [15, 41, 48, 66, 67] . These methods will not be applied in the context of this thesis.

2.2.7: Categorical Data Analysis

Longitudinal data can take either a categorical or a continuous form. Categorical data approaches have been considered by various authors [13, 57, 70]. Chi-squared tests or Fishers Exact tests can be conducted to test the distribution of any categorical variable e.g. the number of abnormal results for individuals. Other methods such as logistic regression could be used to test binary response variables.

The general form of a logistic regression model is:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1\chi_1 + \ldots.\beta_n\chi_n$$

where p is the expected value for the response variable, or probability of having the response. The number of explanatory variables is denoted by n. A maximum likelihood (M.L.E.) approach is taken to estimate the regression coefficients for a logistic model. The response variables are assumed to have a binomial distribution[20].

Hence,

$$p = \frac{\exp^{\beta_0+\beta_1\chi_1+\ldots\ldots\ldots\beta_n\chi_n}}{1+\exp^{\beta_0+\beta_1\chi_1+\ldots\ldots\ldots\beta_n\chi_n}}$$

If there were categorical data with greater than a binary response variable (e.g. age), an alternative approach would be to analyse the variable as a continuous variable. Modelling for categorical data with explanatory variables having greater than a dichotomous response could be conducted using the CATMOD procedure in SAS without having to create dummy variables as is the case when using Proc LOGISTIC in SAS. The main disadvantage over Proc LOGISTIC is the interpretation is not as straightforward. Some manipulation of the output is needed before final results can be obtained [57] . Methods of multivariate testing of categorical data include GEE (developed by Zeger and Liang 1986). The method can be used to conduct regression analysis on repeated categorical (mainly binary/Poisson responses) outcomes. There are macros available to conduct a GEE analysis and these are available in Stokes et al [57]. This GEE method is not addressed in the thesis.

2.2.8: Other Semi-Parametric, Non-Parametric Approaches

Papers have been written on semi-parametric and non-parametric approaches [2, 16, 22].

If one is given samples of sizes $n_1,\ldots.n_k$ from k populations, then the non-parametric Kruskal-Wallis (K-W) test statistic for testing that the populations are identical is:

$$H = \frac{12}{N(N+1)} \sum_{i=1}^{k} \frac{R_i^2}{n_i} - 3(N+1),$$

where

$$N = \sum_{i=1}^{k} n_i$$

and for each i, R_i is the rank sum relative to the observations from the i^{th} population when all the observations are ranked in ascending order from 1 to N. The test here is to reject the hypothesis of equal distribution if H is greater than or equal to the tabulated value.

For the details of various other tests used in this thesis, we refer the reader to standard statistical textbooks and SAS manuals.

2.3 Testing

As can be seen in section 2.2, there are various methods of dealing with repeated measures data and most methods fall into one of the following two categories.

1. Univariate Analysis Methods: including ANOVA [21, 45].
2. Multivariate Analysis Methods[10]: including MANOVA [28,29].

Univariate analysis of variance is a special case of the multivariate analysis of variance approach. Both the ANOVA and MANOVA approaches can be used to test for group differences for the analysis of balanced, continuous repeated measures data and have been mentioned together by several authors[20, 27, 31, 40] . The main aim of any multivariate or univariate testing is to see whether the groups have the same distribution. The following hypothesis is generally tested:

H_0: the treatment groups are homogeneous in nature.

H_1: the groups are inhomogeneous.

2.3.1: Univariate Analysis Methods.

The univariate approach does not account for the factor of time. The aim is to test for differences between average group responses. Methods that are usually used to test for differences are the parametric t-test (using Proc TTEST) to test between the means for two groups or a 1-way ANOVA (using Proc GLM with the RANDOM Statement) for more than 2 groups. If the data is not normal or approximately normal then an equivalent non-parametric test (using Proc NPAR1WAY) would be more appropriate, though one could still use the parametric tests that are robust here. There are generally two methods that could be adopted for this purpose. These are:

a) Univariate testing at each individual time point.

b) Univariate testing on a selected set of single Response Features or Summary Measures (S.M.) that best describes the data as mentioned in [2.2.2].

The first approach treats the repeated measures at each time point as individual measurements and each time point can then be analysed individually. This method was devised at a time when computing resources were limited, and it has many flaws. This is not recommended as a general tool for analysing repeated measures data for a number of reasons. A major assumption here is that each individual has similar times of measurement and this is definitely not always the case. The approach also assumes no relationship or zero correlation between successive measurements, which is also not the case, especially if the repeated measures are measured close together in time. The approach does not account for the continuous nature of the data e.g. if an individual has a significant differences at time 1, 4 and no difference at times 2, 3 and 5. There is no information as to the effect from one time on to the next time results, and also whether there is an overall difference between groups. Information is also not available on when exactly the changes happened over the continuous time scale.

It is also assumed that the data at each individual time point is normally distributed for the purpose of modelling the data. This is obviously not always the case, especially if there are more than two treatments being looked into. Missing data information is ignored in this approach, so if an individual has missing data at times 1, 2, only then the loss of information could be biasing the conclusions when finally comparing the results found at each of the time points 1 to 5 to draw conclusions. The summary measures approach has the main disadvantage of having a loss of degrees of freedom associated with the n individuals, whose summary measures are calculated. Advantages are that the missing data are not an issue here and they are easy to implement. Also, if there are only a moderate number of summary

statistics, then, irrespective of their distributions, there is no loss of generality in assuming their distributions are normal if we are to apply test procedures relative to normal distributions, that are robust.

2.3.2: Multivariate Analysis Methods.

Much of the available literature claims that a univariate approach is not appropriate in most cases while analysing repeated measures data since certain factors are not accounted for. These are things such as the fact that observations that are closer together tend to have a higher correlation than observation further apart in time.

It has been suggested that the MANOVA approach of comparing overall profiles is the only method that requires no knowledge of the general form of the profiles prior to analysis [19,30].

Hence it is often suggested that approaching the analysis in a multivariate manner would often be more appropriate. The approach here is to analyse all the data for an individual as one measurement. Each individual has a p-dimensional vector of repeated measurements at time points t_1 to t_p. Each of the j individuals with data measurements has a vector associated with time. The aim is to test for differences between group means of these vectors. An ANOVA can be conducted on the vector of measurements by treating the multivariate observations per individual as a single measurement. This method is known as MANOVA or multivariate analysis of variance. Greenhouse and Geisser [27] claimed that there were situations when MANOVA was inappropriate. This was if the sample size or number of j individual vectors (e.g. number of patients) within a treatment group was less than the number of parameters or variables available (e.g. number of time points of measurement). The reasoning behind this as mentioned by Kenward [35] was that repeated measured MANOVA can be inefficient if there were more repeated measures than residual df, resulting in a singular variance-covariance matrix and the calculations of the MANOVA statistic becomes invalid.

Likelihood Ratio (L.R.) tests could also be conducted. Both methods assume multivariate normality or, implicitly, the sample size to be large, and test for differences between more than one treatment group. The parametric multivariate methods which can be applied are those based on Hotellings T^2 or equivalently Mahalanobis D^2 statistic which are both used to test the equality of means for two multivariate populations.

The approaches of testing the data are very similar to the univariate procedures in that either of the following methods can be applied:

i) All Times for an Individual analysed together as one observation.

ii) A Combination of Summary Measures analysed together as one observation.

The second approach is not very commonly used but its idea is to analyse a few summary measures that best describe the data together at one time, possibly appealing to the properties of asymptotic tests referred to earlier [section 2.1.2]. These individual summary measures can be analysed together as one combined variable for analysis. The statistical tests mentioned above can be applied to analyse this data.

2.4 Modelling

2.4.1: Covariates and Their Effects Within the Model.

Multivariate methods are commonly used to test for group level differences together with any other covariates that may be considered to have an effect on the outcome variable of interest. In other words, the multivariate approach tests for more than one effect by looking for interactions between the effects and also the individual effects of each covariate of concern. If no interaction exists, then only the individual effects are tested. Examples of some covariates that are commonly tested are 'centre', 'age', 'gender', 'race' etc in addition to the usual main effect of 'group'. If no other effects apart from the main effect 'group' exist and the data are not repeated in time, then the approach would become a univariate ANOVA.

In the case of a profile analysis, where time is also a factor, the problem would immediately turn out to be multivariate in nature. The general aim for the multivariate analysis approach, as for the profile analysis [see section 2.1.3], would be to also test for the effects of 'time' in addition to 'group'. Multivariate modelling techniques can usually be conducted on any longitudinal data set in order to model the response as a linear or non-linear function of time.

There are differences in the effects of the various covariates mentioned above. These are:

(A) 'Time' is repeated on the same individual and the level **changes within an individual** and also **varies between individuals.**

(B) 'Centre' and 'Age' can each have one of two structures. The initial idea, which is easier to analyse, is to assume that both stay **constant within individuals** but **vary between individuals.** This is usually the case for an analysis that does not have the factor of time. This is not always the case in the real world though, especially in the course of a long-term or longitudinal study, where an individual could change centre or get older at each visit. This leads us to the second idea that the variables **change within an individual** and also **vary between individuals.**

(C) 'Gender', 'Race' and in the case of parallel groups randomised longitudinal data sets in particular 'Group', stays constant and never changes for an individual through the course of the study. The variables stay **constant within individuals** but **vary between individuals.**

The general classifications for independent covariates (factors) in repeated measures settings are:

1) **Within-unit factors:** These covariates are time dependent; they vary within units over time.

2) **Between-unit factors:** Specifically baseline covariates, which stay constant over time.

2.4.2: Assumptions.

There are various approaches of modelling multivariate data in time. The general method that takes precedence over ANOVA is the general linear modelling approach of MANOVA. Analysis is usually applied to linear transforms of the data such as means, slopes etc. (using SAS Proc GLM with REPEATED statement, assuming that there is compound symmetry between all measurements and that the data is balanced). For the multivariate analysis of variance approach mentioned above, the general assumption about the variance-covariance structure is that it is a compound symmetric matrix (CS), which is one of the conditions required for the F-test to be valid [see section 2.1.1].

$$\begin{pmatrix} \sigma^2 & \rho\sigma^2 & \dots & \rho\sigma^2 \\ . & \sigma^2 & \dots & . \\ \rho\sigma^2 & . & \dots & . \\ \rho\sigma^2 & \sigma\rho^2 & \dots & \sigma^2 \end{pmatrix}$$

The following three conditions must hold in order for the condition of compound symmetry to hold:

1. Equal variance of repeated measures.
2. Each pair of repeated measures have the same correlation ρ.
3. Also the covariance matrix should be the same for each treatment group.

The usual problem with repeated measures data is that there is typically positive serial correlation between all observation for an individual unit. This therefore does not allow for standard analysis methods of the raw data since the condition of independence between observations is not met. The covariance structure is important in generating a method for the statistical analysis of such data [26]. The main assumption for the model is that treatments are independent of one another. A flexible model for the covariance structure containing both complete and general independence, called Gabriels ante-dependence structure, was the alternative method that was proposed by Kenward [35]. This was believed to be more appropriate for analysing most repeated measures data. Kenward proposed L.R. tests to

compare profiles. The approach was suggested as a way of analysing experiments where no specific features of the profiles were known to be of interest before the results were measured. The structure could be established and a test defined for the overall comparison of profiles under the defined anti-dependence structure. Kenward mentioned that under the condition of general dependence the results correspond to that of the standard MANOVA. Some other approaches have been developed to analyse serially correlated data, when it is known in advance which features of the profile are of interest or which mathematical function could be used to model the data. This is based on the fact that there is a correlation between measurements for models such as random coefficient growth curve and mixed models. This leads us to the area of 'mixed modelling methodology' [section 2.5.2]. Using this method, the parametric structure of the covariance matrix must be stated in advance (using SAS Proc MIXED with REPEATED statement, when the data is not necessarily balanced). Generally, the individuals (patients) yield random effects and the variables (times) or groups (treatments) of measurement have fixed effects. Hence the most appropriate method to deal with repeated measures data would be a mixed model approach [38, 40, 56].

2.4.3: Models

The purpose of modelling any data set is to be able to mathematically reproduce the data. Many papers and talks have been presented on the various modelling techniques available for repeated measures experiments [1, 37, 39, 42, 49, 60, 68]. We will specifically concentrate on models for completely randomised designs [40,70].

Example:

> *Considering the example of heart rate data which is measured for patients, in a completely randomised design, that are each allocated to one of four treatment groups 1 to 4.*

Here treatment is the 'factor' and it has four 'levels'. Let i denote the levels of the factor, j denote the number of individuals within each level of the factor and p denote the number of repeated measurements on each of the individuals. Each individual has a vector of p repeated measurements at t_1 to t_p.
Hence, generally μ_i denotes the mean response of patients treated with drug i=1 to 4 and α_i denotes the effect of drug i where $\alpha_i = \mu_i - \mu$. A factor effect can either be random or fixed.
The overall mean response is μ. Let y be the response variable (for a randomly selected patient on drug i) which is a random variable and has mean μ_i and variance σ^2. The variable y deviates from the mean μ_i by a random amount ε which is a random variable with mean 0 and variance σ^2.

a. Simple Cell-Means Models:

$$y_i = \mu_i + \varepsilon_i$$

For this model, the responses for the heart rate on each drug i=1 to 4 is obtained by adding the fixed mean for the drug and also a random iid error (which is usually assumed to be distributed with $N(0,\sigma^2)$.

b. Simple Factor EffectsModels:

$$y_i = \mu + \alpha_i + \varepsilon_i$$

For this model, the responses for the heart rate on each drug i=1 to 4 is obtained by adding the overall mean and the effects on drug i=1 to 4 and also a random iid error (which is usually assumed to be distributed with $N(0,\sigma^2)$.

c. General Fixed Effects Models:

$$y_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

This model, deals with when each patient is randomly assigned to a therapy. The response for the heart rate are determined for each patient on each drug i=1 to 4 is obtained by adding the overall mean and the effects on drug i=1 to 4 and also a random error. In this case, the response for each patient on the same drug has random variation among patients ε_{ij}. The term ε_{ij} has the same variance for each drug (and is usually assumed to be independent normal) but this is not always the case.

The term 'fixed' effect refers to the situation when all possible levels of the treatments are represented. Using the example at the beginning of this section, the effects are fixed if the four drugs are the only possible levels of therapy and therefore the only information from which conclusions or inferences can be made. For fixed effects model [71], the main purpose is to provide estimates about the group means and differences between them.

d. General Random Effects Models:

'Random' effects models [25] refer to the situation when the levels of the factor used represents only the random sample of a larger set of potential levels. The following structure holds:

$$y_{ij} = \mu + a_i + \varepsilon_{ij}$$

Here μ represents the overall population mean. If drug is a random factor, then a_i represents the independent random effects of the drug that are random variables with mean 0 and variance σ_T^2. In this case ε_{ij} are independent random variables with mean 0 and variance σ^2 (usually taken to be normal) and hence, the variance of a randomly chosen individuals response is $\sigma_T^2 + \sigma^2$.

e. Mixed Effects Models.

This is a combination of the general random and fixed effects models.

As the name suggests, the model consists of both random and fixed effects. The following expression shows the general structure of a mixed model for repeated measures analysis:

$$y_{ijk} = \mu + \alpha_i + \gamma_{ik} + \tau_{ij} + \varepsilon_{ijk}$$

Here μ would be the grand mean, α_i would represent fixed group effects, γ_{ik} would be the group by time interaction effects, τ_{ij} would be mutually independent random effects for subjects within groups and ε_{ijk} would be mutually independent random measurement errors. All τ_{ij} are identically distributed and so also are all ε_{ijk}, and all τ_{ij} and ε_{ijk} are mutually independent (usually assumed to be normal with zero mean).

A generalisation of the model above is when the vectors $(y_{ij1},....y_{ijp})$ are mutually independent, and for each treatment group i, are identically distributed. This is one of the most general parametric models and versions of this model will be used in chapter 8, to analyse the data sets used for this thesis.

Other modelling approaches such as survival analysis [section 2.2.5] and logistic regression [section 2.2.7] approaches can also be investigated to get a better understanding of the data sets.

2.5 Discussion

Researchers have suggested repeated measures analysis methodology that can be anything from extremely simple to very complex to implement. Everitt [19] produced a very good review paper of the analysis of repeated measures data. The paper summarises some of the suggested most popular methods of analysis.

We should note that often complexities in the structure of the data itself could lead to difficulties with data analysis. A useful condition is to conduct a balanced complete blocks design when setting up a design to collect repeated measures data. Most papers agree that the first thing to do as with any data analysis is to get a feel for the data and conduct some sort of initial exploratory data analysis. The best way of doing this is to present it in some graphical manner (e.g. correlogram, scatter plot, box-plot, CI and mean plot). Summary measures can also be obtained. Once plots have been produced one can see changes on unusual happenings with the data.

A major issue in the analysis of R.M. data is the issue of data distributions being normal and also that there is independence and identical distributions between successive time measurements. All methods

mentioned so far are on how to deal with continuous data. The methods of analysing continuous data vary. Usual methods of modelling continuous data would be using linear or non-linear models with random and/or fixed effects.

The multivariate tests based on the p-dimensional vectors for patients tend to be unreliable especially if p is large and the normality assumption is not met. On the other hand, reduced data involving only one or two summary measures throw away a vast amount of information, but the test procedures in this case tend to be robust and do not heavily depend on the normality assumption. We should therefore use a compromise and one of the major contributions of the present thesis is to suggest ways of analysing the data based on a reduced set of observations or a set of summary measures so that as much of the overall information from the data is retained. We use robust test procedures that do not stringently depend on the assumption of normality.

As implied earlier, to arrive at reasonable conclusions even with non-parametric or categorical data, one can not allow too many repeated measures, and hence one must find ways of reducing the value of p. Of the categorical and non-parametric tests that will be encountered in this thesis we include tests of homogeneity for the distribution of the number of abnormal readings in various treatment groups, and the Kruskal-Wallis test for investigating whether different treatments perform differently.

One could also undertake more complex investigations, involving categorical data with higher dimensional tables and various levels of abnormality, for testing homogeneity for treatments. However, this is beyond the scope of the present study.

2.5.1: ANOVA vs. MANOVA

Some early work on profile data analysis was conducted by Greenhouse and Geisser [27] who together wrote a social sciences paper on the methodology used to analyse profile data. The paper referred to mainly works on univariate ANOVA, MANOVA and other statistical methodology for multivariate research [31]. The aim of the paper, even though showing multivariate techniques, was to show that ANOVA was the easiest way of dealing with the multivariate data set that was being analysed. The authors specifically looked into the how the F statistics could be adjusted according to the assumptions being made about the variables of interest. They claimed that the univariate ANOVA approach allowed analysis of data that could not be analysed using multivariate methods. Details of when this would be the case are given below.

There has been a great deal of discussion for many years on the issue of whether to use the classical univariate analysis of variance (ANOVA) method [5, 21, 23] or the generalised multivariate analysis of variance (MANOVA) [28, 29] method to analyse such data. There are advantages and disadvantages to both methods. The main problem with the univariate approach is that it assumes independence or zero correlation between successive measurements. Univariate ANOVA does not account for the fact that measurements that are closer together usually tend to be more closely related (highly dependent), leading to larger correlations, than those measurements further apart and also for the fact there is variability between experimental units.

The main problems with multivariate methods on the other hand are that they are much harder to implement than univariate methods. The results are also not reliable if the data is not approximately multivariate normal especially if the tests used are non-robust. For repeated measures MANOVA, no assumptions are made about the covariance structure of repeated measures and therefore all variance and covariance parameters need to be estimated. A typical case when MANOVA techniques would not be appropriate would be if the sample size or number of j individual vectors (e.g. number of patients) within a treatment group i was less than the number of p parameters or variables available (e.g. number of times of measurement)[27]. Along similar lines, repeated measured MANOVA can be inefficient if there are more repeated measures than residual df since there will be a singular variance-covariance matrix and the MANOVA statistic can not be calculated[18,35]. Multivariate normality is harder to test for than univariate normality. For this thesis, a data reduction approach was suggested so that the condition of asymptotic normality could then be applied and hence the test results would become valid.

Since the conditions of normality, equal variance and mutual independence or zero correlation were not always reasonable, especially if there were more than two treatment groups or schedules to compare Greenhouse and Geisser [27] made one assumption about the variables of interest in order to conduct the univariate ANOVA. This was that they had a multi-normal distribution with arbitrary variance-covariance matrix. The problem of multivariate observations was approached in a general way and it was assumed that an individual vector of 1 to p observations for each individual was sampled from a p-variate normal distribution with an arbitrary variance-covariance matrix. In other words, the p observations were assumed to be jointly normal (i.e. p-variate normal) with no assumptions being made about the variance-covariance matrix.

Block et al [4] also used the ANOVA approach but they used assumptions of equal variances for all variables and also of independence (or equal correlation between variables).

Greenhouse and Geisser extended the work of Box [5,6] on the approximate distributions of F statistics in ANOVA for one group to the case of several groups. The df were adjusted for the approximate F tests to get more conservative tests which could be used when the variance-covariance matrices differs from group to group if the sample size of groups were the same.

2.5.2: Mixed Modelling

The Mixed Modelling approach deals with some of the shortcomings associated with both the ANOVA and generalised MANOVA methods. The model would consist of both fixed and random effects that would best describe the data. A mixed models method of dealing with repeated measures data would need a prior knowledge of the covariance structure before the time of analysis (a priori) in order to fit the model.

In the past, the multivariate method of mixed modelling was not a feasible option since it was computationally challenging. In recent years, SAS procedure MIXED [52] has been devised to deal with this particular type of analysis. A useful reference is the book in the series by SAS user's [40]. The book gives a range of practical methods and techniques to deal with data for mixed modelling and has a chapter devoted to repeated measures analysis. The SAS procedure is very extensive in its coverage and only a specialised part of its capabilities has been used for this thesis.

Many authors have suggested that the covariance structures play an important role in the modelling of any repeated measures profile data. In conducting multivariate analysis using a mixed modelling approach, one of the major assumptions is that the correct covariance structure needs to be specified and built into the model at the time of analysis in order to get valid results for the data [26,46,65]. SAS Proc MIXED has a range of possible covariance structures built in as options. The main ones typically referred to are the following: 'UN' which is the unstructured matrix, 'CS' is the compound symmetric matrix, AR (1) and AR (1) with a random effect, 'SIMPLE' is the simple matrix.

The random effects in the model structure are affected by the fact that measurements closer together in time have higher correlations than measurements further apart. This is the reason that the covariance structure must be built into the mixed model. If this were not done, invalid results would be obtained. The general SAS command used for mixed modelling of repeated measures data is Proc MIXED with the REPEATED statement.

2.6 SAS Procedures Used

SAS version 6.10 on VMS and later 6.12 on UNIX were used for analysis of the data. Programs produced are displayed in Appendix B. SAS manuals can be referred to for all details on any procedures mentioned [50-55]. The main SAS procedures used for analyses are as follows:

Proc UNIVARIATE with *normal* option: produced univariate normal tests.

Proc MEANS: produced Summary Measures.

Proc FREQ: produced frequencies. The *chisq* options ⇒ Chi-squared tests. The *exact* option⇒ Fishers exact tests for some situations and the *cmh* option ⇒ Mantzel-Haenzel tests.

Proc PRINCOMP: used to conduct the P.C.A. ⇒ eigen-values, vectors and principal components.

Proc DISCRIM with *distance* option: computes Mahalanobis distances^2 between each pair of treatment groups.

NOTE: Both PRINCOMP and DISCRIM drop any observations with at least one missing record from the analyses.

Proc NPAR1WAY: computes either Wilcoxon (for 2 groups) or Kruskal-Wallis tests (for > than 2 groups).

Proc GLM: computes both ANOVA and MANOVA. Only ANOVA results are valid when unbalanced groups exist. In the case of univariate ANOVA, Proc GLM is advantageous over Proc ANOVA (which does not handle unbalanced groups). The MANOVA is not valid with unbalanced groups and individuals with missing data are also dropped from the analysis.

Proc MIXED: was specially devised to handle mixed modelling but the procedure can be used in place of Proc GLM to analyse multivariate data. The advantage over proc GLM is that it deals with missing data and unbalanced data if it is missing completely at random (MCAR).

Proc MIXED and Proc GLM, while trying to conduct similar analyses, use different estimating procedures. Proc GLM uses Method Of Moments (MOM) estimation to obtain ratio of means squared (F) statistics and Proc MIXED uses Maximum Likelihood (MLE) or restricted residual MLE (REML) methods and Wald-type F statistics [40, 52, 70].

Proc LIFETEST: computes Kaplan-Meier estimates for time to incidence data and also computes L.Ratio tests.

Proc LOGISTIC: computes logistic regression odds ratios for binary response variables.

2.7 Overview

In the previous chapter we have discussed various statistical methods to deal with longitudinal data structure analysis. The key methods to analyse continuous data, which will be used further on in this thesis, include plotting the data, response features approach and discriminant analysis. The methods used for the categorical data include logistic regression and survival analysis techniques.

In the next chapter, we will discuss the data sets used for this thesis and also any problems that were encountered during data analysis.

CHAPTER 3: The Observed Data and Basic Summary Measures.

3.0 Introduction

This chapter introduces the reader to the actual data to be used for analysis. There are two continuous data sets A and B. Data set A contains vital sign measurements for 86 patients each randomly allocated to one of four treatment groups and two centres. Data set B contains dietary response measurements for 24 individuals randomly allocated to one of three diets. In addition, data set A is further classified as a categorical data set.

The multivariate and univariate structure of each continuous data set and the univariate structure of the categorical data set are described in this chapter. Also mentioned are all the univariate summary measures obtained from each data set.

Listings 3.1.1 to 3.5, in this chapter, show the data structure of the first few observations of several data formats that will be used during the analysis.

3.1 Observed Data Structures

3.1.1: Description of the Observed Data Sets.

There were two repeated measures data sets each having a longitudinal design. These were:

3.1.1.1 Data Set A: A large real data set containing 24 hour Ambulatory Vital Sign Readings.

This was a blinded data set that was provided by SANOFI UK Ltd. (1994).

The design was a parallel groups design. A total of 86 patients were selected from one of two centres (1 or 2) and the patients within each centre were randomly allocated to one of four treatments (1,2,3 or 4). The two covariates in this data set are 'centre' and 'drug' and both stay constant through the study. Baseline measurements of the three independent response variables systolic blood pressure, diastolic blood pressure and heart rate were taken for each individual before active therapy was administered. Once therapy was administered, readings of the same 3 variables were again measured at 24 separate time points using an ambulatory monitoring system that was attached to each individual patient. The patients were not balanced between centres or overall treatment groups. On a few occasions the system failed and so a set of measurements (at that failed time point) were not available.

NOTE: Things which were unknown about the study were the times of start and stopping the therapy, and whether or not there was more than one administration of the therapy during the 24 points of measurement. The age of individuals both at baseline and at each time point was also unknown. These

are all variables that would have been useful to know. It was assumed that these readings were taken for 24 hours at equally spaced hourly intervals. Listing 3.1.1 below shows the layout of the univariate data set A by displaying some of the vital sign data in a univariate format for one patient (ID=10013).

Listing 3.1.1
Univariate Data Structure: Data Set A (Systolic Blood Pressure (mmHg))

MEASURE	DRUG	PATIENT	CENTRE	BASE	TIME	VALUE
SBP	2	10013	1	154.787	0	154.79
SBP	2	10013	1	154.787	1	165.75
SBP	2	10013	1	154.787	2	171.00
SBP	2	10013	1	154.787	3	157.00
SBP	2	10013	1	154.787	4	153.75
SBP	2	10013	1	154.787	5	160.00
SBP	2	10013	1	154.787	6	152.75
SBP	2	10013	1	154.787	7	166.25
			...			
SBP	2	10013	1	154.787	24	141.25

continued..

Displayed on the next page in Listing 3.1.2 are the heart rates for three individuals (ID=10001, 10009 and 10011) in data set A shown in a multivariate format.

Listing 3.1.2
Multivariate Data Structure: Data Set A (Heart Rate (beats/min)).

MEASURE	DRUG	CENTRE	BASE	PATIENT	_0	_1	_2	_3	_4	_5	_6	_7	_8	_9	_10	_11
HR	1	1	70.0958	10001	70.10	74.50	75.00	90.33	78.75	82.00	81.25	88.00	80.75	89.33	82.33	91.00
HR	1	1	70.7569	10009	70.76	61.00	56.50	81.00	81.75	62.50	62.33	76.00	76.67	102.50	71.00	82.75
HR	1	1	71.2431	10011	71.24	.	74.67	64.25	64.50	69.75	64.50	73.25	79.50	123.00	75.75	90.67

continued ..

MEASURE	DRUG	CENTRE	PATIENT	_13	_14	_15	_16	_17	_18	_19	_20	_21	_22	_23	_24
HR	1	1	10001	77.50	75.00	67.50	70.0	77.0	79.0	78.00	85.0	94.0	81.00	102.00	85.33
HR	1	1	10009	64.00	65.50	64.50	66.5	59.5	69.5	72.00	63.0	59.5	60.50	115.00	97.00
HR	1	1	10011	71.50	78.00	71.50	60.5	65.5	61.0	57.50	57.0	64.5	60.50	59.50	63.50

continued ..

3.1.1.2 Data Set B: A small randomly generated data set of responses on 3 combinations of therapy.

This data set of a parallel groups design study was randomly generated by Dr. Roy Saunders, SANOFI Research, USA (1997). There were 24 individuals and they were randomly allocated to three treatment groups. These were diet, diet+drug1, diet+drug2. Treatment was the only covariate of interest for this data set. Recordings of the response variable, dietary response was taken at 10 time points. There were no other variables measured. The data was a balanced design with 8 individuals in each group. There were some missing responses within the data set. Listing 3.2.1 below shows a univariate listing of all of the dietary response values for one subject in data set B (ID=1).

Listing 3.2.1
Univariate Data Structure: Data Set B (Dietary Response)

GROUP	SUBJECT	BASE	TIME	RESPONSE
Group1	1	1.12598	0	1.13
Group1	1	1.12598	1	0.94
Group1	1	1.12598	2	0.98
Group1	1	1.12598	3	0.87
Group1	1	1.12598	4	0.89
Group1	1	1.12598	5	0.88
Group1	1	1.12598	6	1.15
Group1	1	1.12598	7	1.11
Group1	1	1.12598	8	1.00
Group1	1	1.12598	9	0.95

continued.

Listing 3.2.2 shows dietary response data in multivariate format for 5 individuals (ID=1,2,3,4,5) in group 1

Listing 3.2.2
Multivariate Data Structure: Data Set B (Dietary Response)

GROUP	SUBJECT	BASE	_1	_2	_3	_4	_5	_6	_7	_8	_9
Group1	1	1.12598	0.94	0.98	0.87	0.89	0.88	1.15	1.11	1.00	0.95
Group1	2	0.94240	0.78	0.81	0.73	0.84	0.94	0.82	0.89	0.80	0.94
Group1	3	0.81512	0.74	0.75	0.74	0.92	0.95	.	0.95	0.98	0.77
Group1	4	0.87353	1.02	0.96	0.83	0.83	1.08	1.02	1.12	1.02	1.04
Group1	5	1.00571	1.09	1.01	0.90	0.85	0.85	1.04	1.02	1.13	1.01

continued ...

3.1.2: About the Observed Data Sets.

As can be seen above, permanent SAS files named 'UNI_1' (for the univariate structure) and 'MULT_1' (for the multivariate structure) were created for both of the original data sets A and B. The variable 'BASE' was equivalent to the measurements at 'TIME'=0 and this measurement was the pre-treatment baseline reading. All other readings that were measured were recorded on-treatment.

Similarities between data sets A and B were:

a) They were both longitudinal in nature.

b) Both data sets had missing records. Data set A had missing data for 13 of the 86 individuals in the study. There were also 2 additional patients with missing baseline data. Data set B had missing data for 4 out of 24 individuals in the study. The times and patients with missing data are mentioned in section 4.2.

c) Both data sets were unbalanced following the missing data records.

d) Both data sets had less individual profiles in a treatment group than actual number of repeated measurements (times) being measured.

There were some obvious differences between the observed data sets:

a) Data set A was 'large', whereas data set B was 'small'.

b) Data set A had 3 variables being measured (HR, SBP and DBP), whereas data set B had only one variable (dietary response).

c) Data set A had many repeated observations being measured (24 equally spaced time points and baseline) and there were many individual profiles (22 or 21) in each of 4 treatment groups. However, data set B had only a few observations being measured (10 equally spaced time points) and there were a few individual profiles (8) in each of 3 therapy groups.

3.2 Classification of Vital Sign Data

This refers to data set A only since categorical information was unavailable for data set B.

All categorical methods were applied to only the original data set A1 before missing data was generated.

Data was categorised into 7 groups according to the National High Blood Pressure Education Program, JNCV Report medical literature on blood pressure and heart rate normal ranges as displayed in Table 3.1.1 below. It was mentioned within the report, that low blood pressure would not usually be of considerable concern for a patient's health. Except in rare cases a low blood pressure is good for ones blood vessels and heart. Abnormally 'high' results for blood pressure is known as 'hypertension' and

this is something which is considered serious as the numbers become higher. Systolic blood pressure would usually increase due to hunger whereas diastolic blood pressure would remain constant in this situation. Low heart rates are usually found in athletic individuals and are not usually of concern. Medications that would decrease heart rate would be beta-blockers. Higher pulse rates usually indicate some sort of stress on the heart and are something to worry about. Slight increases in heart rate can occur if an individual is hungry. Other things that could increase heart rate would be exercise or medications such as calcium channel blockers. The ranges are as follows:

Table 3.1.1
Seven Stage Vital Sign Classifications

Category Age : 18 years old over	Heart Rate or Pulse (beats/minute)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Low	40-59	80-99	40-59
Normal	60-79	100-129	60-84
High Normal	80-99	130-139	85-89
***High: Stage 1**	100-119	140-159	90-99
Stage 2	120-139	160-179	100-109
Stage 3	140-159	180-209	110-119
Stage 4	160 or over	210 or over	120 or over

* Note: High for Blood Pressure would be hypertension. The categories for blood pressure are from the National High Blood Pressure Education Program, JNCV Report.

Heart rate information was obtained after consultation with an M.D [69].

The data was further classified into the following 3 groups using the classification above:

Table 3.1.2
Normal, High and Low Vital Sign Classifications.

Category	Heart Rate or Pulse (beats/minute)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Low	< 60 (Bradycardia)	< 100	< 60
Normal	60-99	100-139	60-89
High	100 or over (Tachycardia)	140 or over	90 or over *

* Note that the definition used for 'High' diastolic blood pressure is based on the old definition by the American Heart Association.

The following listing shows the categorical data set structure by displaying some of the observations for one patient (ID=10001) following the classifications mentioned above. Here time is displayed in a univariate manner.

Listing 3.3
Categorical Data: Original Data ONLY for Data Set A (Vital Signs Data)

DRUG	CENTRE	PATIENT	TIME	ABNORMAL	CATEGORY	LOW	HIGH	NORMAL
1	1	10001	1	Normal	Normal	No	No	Yes
1	1	10001	2	Normal	Normal	No	No	Yes
1	1	10001	3	Normal	High Normal	No	No	Yes
1	1	10001	4	Normal	Normal	No	No	Yes
				. . .				
1	1	10001	24	Normal	High Normal	No	No	Yes
1	1	10001	0	Normal	Normal	No	No	Yes

continued ..

Vital sign categories and ranges were obtained from Tables 3.1.1 and 3.1.2 above. The variable 'CATEGORY' was created by giving each test result a value of 1 to 7 or missing using the normal ranges displayed in Table 3.1.1. Since there were far too many categories to conduct any tests, another variable 'ABNORMAL' was created. This variable had three levels (low, normal and high) together with missing data and the ranges used are given in Table 3.1.2 above. In addition, three binary response variables ('LOW', 'NORMAL' and 'HIGH') were created for every time point using variable 'ABNORMAL'. In each case the variable had a value of 1 for "yes" and 0 "otherwise". These three variables each had a complete set of records for each patient since missing data was given the value 0 for "no" event. The data set therefore had a total of 24 "yes" or "no" on-treatment response variables per individual. These corresponded to the individuals 'on-treatment' readings at time 1 to 24. Each individual also had a single "yes" or "no" response variable at baseline. Listing 3.3 above shows one page of the structure of this categorical data set.

3.3 Univariate Summary Measures

3.3.1: Continuous Summary Measures.

Univariate summary measures were obtained for both continuous data sets A and B described above in Listings 3.1.1 and 3.2.1 respectively. There were 7 univariate summary measures that were used during data analysis. These measures were the mean, median, minimum, maximum, upper and lower quartiles as well as the change in mean on-treatment observations from the baseline observation. The formats of the data sets of summary measures are displayed below in Listings 3.4.1 and 3.4.2 below for data set A and B respectively.

Listing 3.4.1
Summary Measures By Patient and Drug: Data Set A :Heart Rate (beats/min): Original Data Set

DRUG	CENTRE	PATIENT	MEAN	MEDIAN	MIN	MAX	Q1	Q3	BASE	CHANGE
1	1	10001	82.1	81.1	67.5	102.0	77.3	87.5	70.1	12.1
1	1	10009	72.8	68.0	56.5	115.0	62.4	78.8	70.8	2.0
1	1	10011	70.2	64.5	57.0	123.0	61.0	74.7	71.2	-1.1
					...					
1	1	20017	66.9	67.1	58.0	81.3	63.3	70.8	66.1	0.7
1	2	20028	66.3	64.5	54.0	92.5	61.5	69.1	65.8	0.5

continued ..

Listing 3.4.2
Summary Measures By Subject and Dietary Group:Data Set B (Dietary Response): Original Data

GROUP	SUBJECT	MEAN	MEDIAN	MIN	MAX	Q1	Q3	BASE	CHANGE
Group1	1	1.0	1.0	0.9	1.1	0.9	1.0	1.1	-0.2
Group1	2	0.8	0.8	0.7	0.9	0.8	0.9	0.9	-0.1
Group1	3	0.9	0.8	0.7	1.0	0.7	1.0	0.8	0.0
Group1	4	1.0	1.0	0.8	1.1	1.0	1.0	0.9	0.1
Group1	5	1.0	1.0	0.9	1.1	0.9	1.0	1.0	0.0
Group1	6	0.8	0.8	0.6	0.9	0.7	0.9	0.9	-0.1
Group1	7	0.9	0.9	0.7	1.2	0.8	1.0	1.0	-0.1
Group1	8	0.9	1.0	0.8	1.1	0.8	1.0	1.1	-0.1
Group2	9	0.7	0.7	0.5	0.9	0.6	0.8	1.1	-0.5
Group2	10	0.8	0.8	0.7	1.0	0.7	0.9	1.1	-0.3

continued ...

3.3.2: Categorical Summary Measures.

The categorical data in Listing 3.3 above was further broken down into univariate summary measures in order to be used for analysis. The number of positive 'on-treatment' responses, per patient, was tallied for each of the three binary variables, 'LOW', 'NORMAL' and 'HIGH', to create the three variables 'NL', 'NN' and 'NH' respectively. Each individual had a value for each of these variables that could range anything from 0 to 24. The three variables could add up to no more than 24, since the sum was the number of available 'on-treatment' readings.

From reading through the available literature, it became apparent that only 'HIGH' results were considered to be truly abnormal results. Hence all further categorical analyses were conducted by considering only 'HIGH' results to be abnormal. Both 'HALFABN' and 'QRTABN' were similar measurements. Both were dichotomous yes/no response variables. The initial variable measured whether more than 50% of the results were abnormal and the second variable measured if more than 75% of results were abnormal.

The frequency of abnormally 'high' results per individual are displayed for three individuals (ID=10001,10009,10011) in Listing 3.5 below. In the listing below, 'FREQ' was missing since it was only calculated for systolic and diastolic blood pressure and not for heart rate data. This variable would take the values 0-12,13-18 and 19-24 where these are the ranges of number of 'high' (abnormal) responses per individual. The reason for 'FREQ' not being calculated for HR was that the maximum number of abnormally 'high' HR readings per individual was 6 and hence no comparisons could be made between treatment groups. Hence, a second variable 'FREQ2' was calculated where the values were 0, 1-3 and 4-6 respectively.

Listing 3.5
Number of Abnormal Readings Original Data ONLY for Data Set A: Heart Rate Data

DRUG	CENTRE	PATIENT	N	HALFABN	QRTABN	NL	NN	NH	FREQ	FREQ2
1	1	10001	24	No	No	0	23	1	.	1-3
1	1	10009	24	No	No	3	19	2	.	1-3
1	1	10011	23	No	No	3	19	1	.	1-3

continued..

3.4 Overview

The previous chapter describes the structure of the data sets that were analysed for this thesis. There are two data sets A and B [section 3.1] and both contain response variables that were continuous in nature. The three response variables in data set A can be further classified into categorical variables using ranges obtained from the definition for the American Heart Association [section 3.2].

SAS version 6.10 on the VAX mainframe and later SAS 6.12 on a UNIX platform were used to analyse the data. Any important SAS programs are displayed in Appendix B.

The following chapter 4 explains the exploratory data analysis (EDA) conducted on the data and any univariate statistical tests applied to the data. Also mentioned are problems encountered with the data together with any solutions. Each of the three continuous response variables (heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP)) in data set A, were analysed as separate individual outcome variables. Any continuous data analysis methods conducted on the data sets were identical for all three of these variables. Both the continuous ambulatory measurements in data sets A (Listing 3.1.1 and 3.1.2 above) and the dietary response in data set B (Listing 3.2.1 and 3.2.2 above) were each analysed using continuous data analysis methods. In addition, the variables in data set A were also analysed as both categorical and continuous variables following a categorical classification.

CHAPTER 4: Exploratory Data Analysis

4.0 Introduction

The previous chapter introduced the reader to both the univariate and multivariate structures for the two continuous longitudinal data sets A and B that were used for study in this thesis. Also suggested were various univariate summary measures that could be used to describe the data.

All approaches used were applied to both data sets A (three vital sign variables heart rate, systolic and diastolic blood pressures) and B (dietary response) unless otherwise stated. During the analysis, the four aforementioned variables were considered to be four independent variables and hence analysed as such.

Note: Any relevant SAS code required for analysis is given in Appendix B.

Within this chapter, an initial exploratory data analysis was conducted on the original data sets in their univariate format, in order to gain initial feeling for how this data was behaving over time.

There was the problem of missing data, which would not affect any univariate methods but would definitely have an impact on any future multivariate analysis methods. A generated data set was created for analysis purposes by replacing as many of the missing records as possible.

Any univariate plots (Figures 4.1.1 to 4.4.4 below) were produced in order to get an idea of the behaviour of the data sets at both baseline (pre-treatment) and at each individual (on-treatment) time point. All the univariate plots over time, which were created for the original data sets were also produced for the data sets after imputing missing data. It was found that there were not any detectable differences in the plots when comparing plots of before and after data imputation. Since there were no vast differences between the two sets of figures, as was also the case with the univariate tests, the only figures displayed are those produced from the original data sets.

4.1 Profile Plots of the Continuous Data Over Time

Initially, as most of the literature suggests, individual profile plots were plotted to show the behaviour of each of the individuals data over time. For both data sets A and B, there were far too many patients in the study to be able to distinguish clearly between treatment groups when all the data was plotted on one graph. Hence, a separate profile plot was produced below for each of the four treatments (Figures 4.1.1 to 4.1.3) in data set A or three therapy groups in data set B (Figure 4.1.4). Even after plotting the data in this manner, it can be seen that all these plots are still very cluttered and difficult to interpret. The only use in these plots is to gain a general feel for how the data is behaving for each individual. It is recommended that other types of plots such as box-plot summaries or summary plots such as those

produced in sections 4.2 and 4.4 respectively be used in place of the individual profile plots while trying to interpret the data and distinguish between the behaviour of treatment groups.

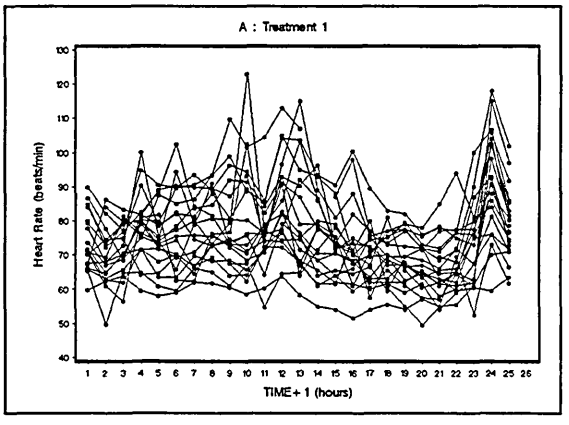
4.1.1: Heart Rate (beats/minute):

Figures 4.1.1 A-D below show the individual patient profiles displayed by each respective treatment group 1 to 4 for the original heart rate (beats/minute) data.

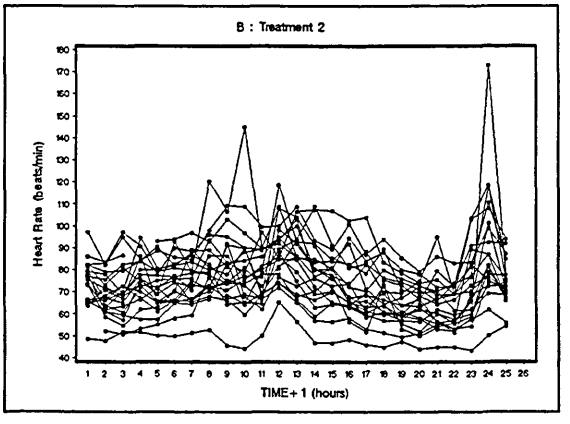
Even though a separate plot was produced for each treatment group, the figures were still very congested and difficult to interpret. By initially eyeballing these four figures the initial thing that was noticed was that individuals on drug 4 appeared to have heart rates that were more spread apart than any of the other treatment groups. However, when looking at the scale of the plots it was found that drug 2 in fact has a greater spread in it's data and this was only the case due to one supposed outlier at time 22 hours on-treatment. However, since this was not determined to be an outlier, the measurement was kept in the analysis. There was also one individual that had consistently lower readings than all other individuals on drug 2. All treatments appeared to dip at around 14 or 15 hours and then peak at around 23 hours.

FIGURE 4.1.1
Individual Patient Profiles of Heart Rate over Time by Treatment Group.
Original Data: Before Missing Data Replaced (N=86).

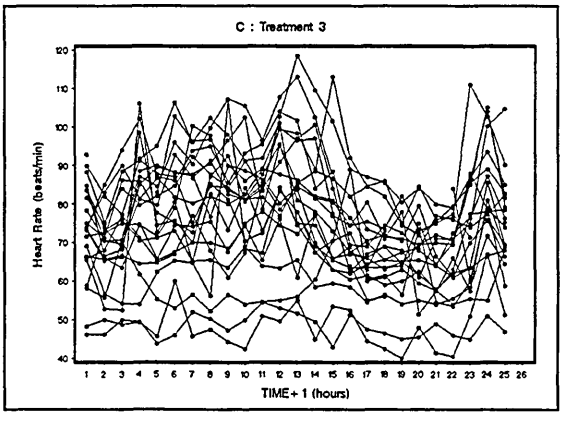
A: Treatment 1



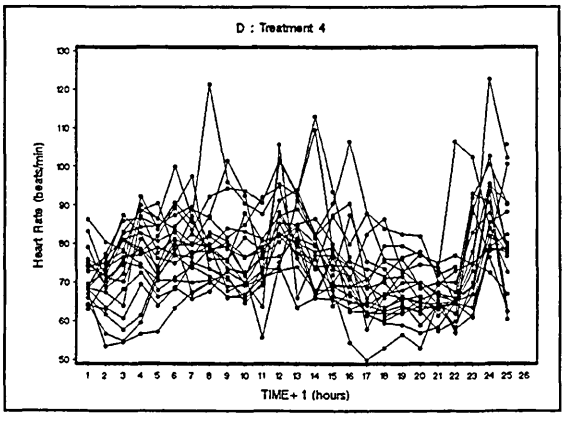
B: Treatment 2



C: Treatment 3



D: Treatment 4



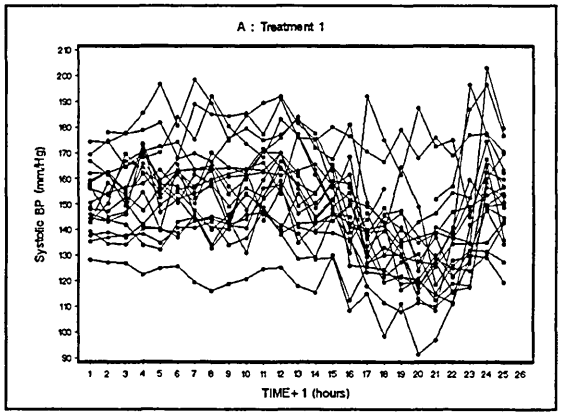
4.1.2: Systolic Blood Pressure (mmHg):

Figures 4.1.2 A-D below show the individual patient profiles over time displayed by each of four respective treatment groups 1 to 4 for the original systolic blood pressure (mmHg) data.

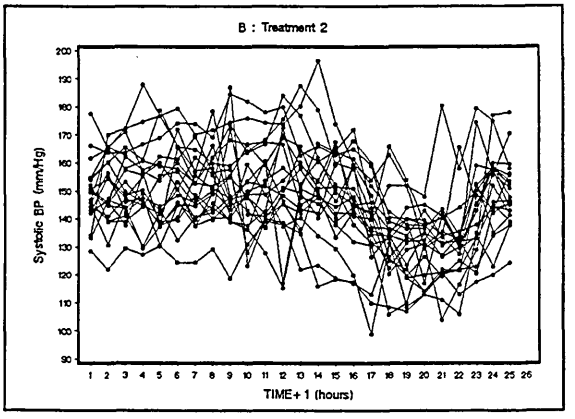
These plots were produced before imputing missing records. Each treatment group was very congested. None of the plots have a pattern that can easily be described. The readings for drug 4 were on the whole lower than readings for the other three treatments. It can be seen that drug 4 has smaller variation in the data as opposed to drug 3. There was a dip in the data around time 22 hours for drug 4. The data for drug 4 had a smaller range than all the other three treatments. Drugs 1 and 3 each had one individual that appeared to have a set of extremely low readings. These could be outliers but they were not omitted from any analyses.

FIGURE 4.1.2
Individual Patient Profiles of Systolic Blood Pressure over Time by Treatment Group. Original Data: Before Missing Data Replaced (N=86).

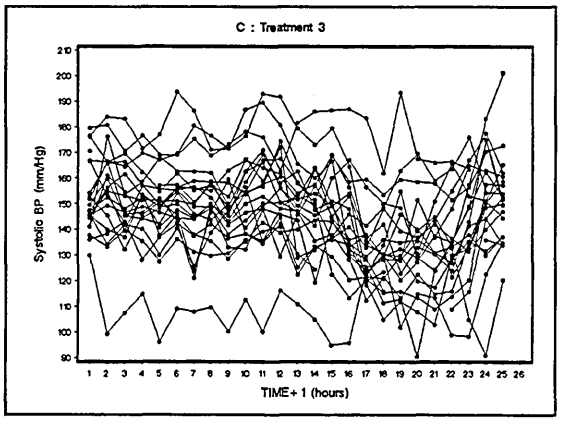
A : Treatment 1



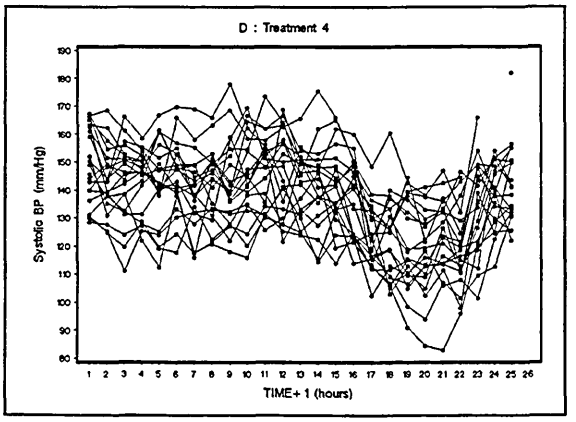
B : Treatment 2



C : Treatment 3



D : Treatment 4

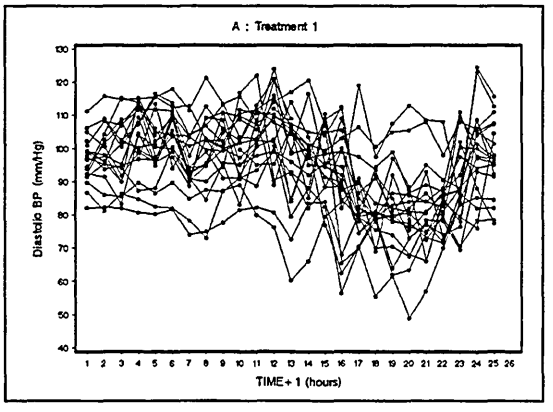


4.1.3: Diastolic Blood Pressure (mmHg):

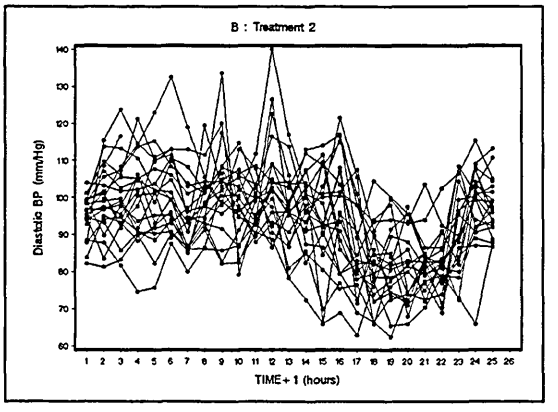
Plots of the individual patient profiles over time were displayed below for diastolic blood pressure by treatment groups (Figures 4.1.3 A-D). These plots were produced before imputing missing records. Each plot appeared very cluttered. None of the plots have a pattern that could easily be described. Drug 2 tended to have individuals with slightly larger diastolic blood pressure readings on average than any other treatment group.

FIGURE 4.1.3
Individual Patient Profiles of Diastolic Blood Pressure over Time by Treatment Group. Original Data: Before Missing Data Replaced (N=86).

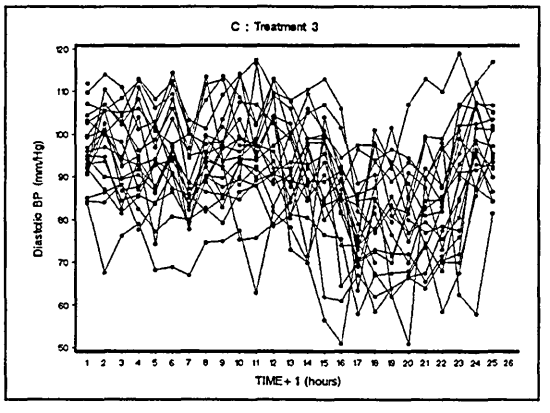
A : Treatment 1



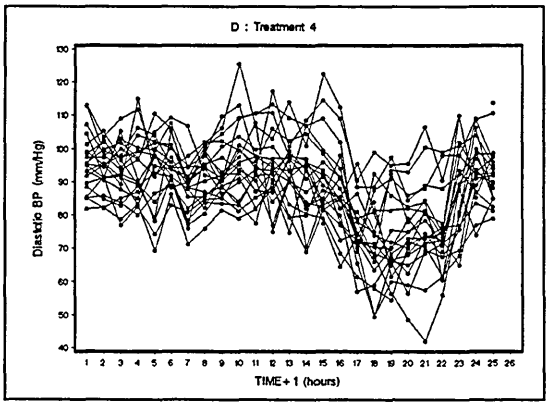
B : Treatment 2



C : Treatment 3



D : Treatment 4

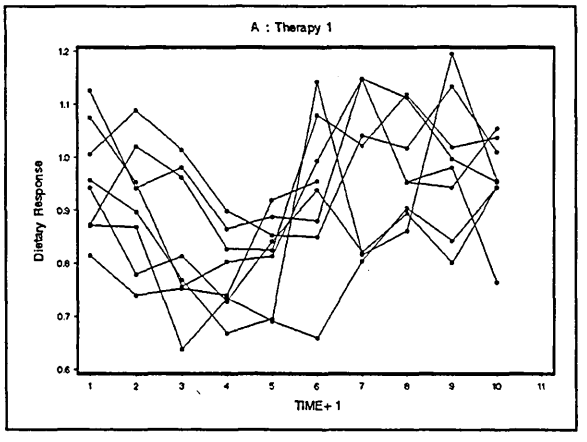


4.1.4: Dietary Response

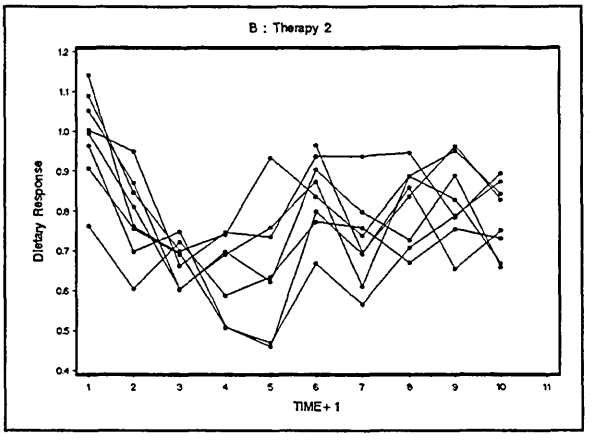
Figures 4.1.4 A-C below show the individual patient profiles displayed by each of three respective therapies for the dietary response data. From the individual profile plots below, it can be seen that therapy 1 is varying a great deal between individual responses. For therapy 2, the observations are closer together but there is still some variation at certain times. For therapy 3, the observations are very close together with little variation at each time point. There are obvious differences in profiles. Therapy 3 is very different from the other two therapies.

FIGURE 4.1.4
Individual Patient Profiles of Dietary Response over Time (hours) by Therapy Group: Original Data: Before Missing Data Replaced (N=24).

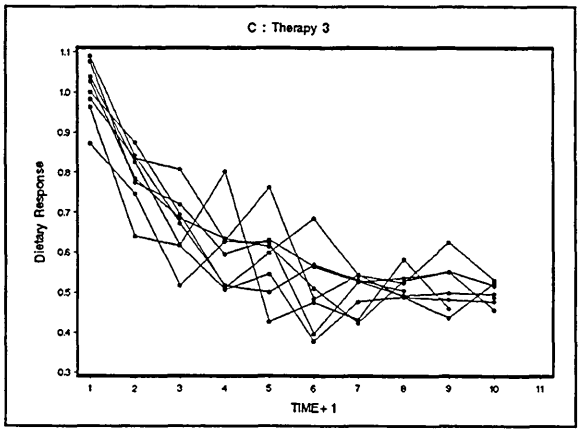
A : Therapy 1



B : Therapy 2



C : Therapy 3



4.2 Missing Data Records Over Time

4.2.1: Missing Data Patterns

It could be seen from the individual profile plots 4.1.1-4.1.4 above that some of the individuals in both studies did not have a complete set of records. Both data sets A and B had missing records, which in turn lead to an unbalanced design in both cases. These missing data patterns are described in Tables 4.1.1 and 4.1.2 below for data sets A and B respectively. Data Set A had missing on-treatment records for 13 patients and missing baseline records for 2 patients (Table 4.1.1). The same observations were missing for all three variables HR, SBP and DBP indicating that the machinery had failed at these specific times. Data Set B had missing on-treatment records for 4 patients (Table 4.1.2).

Table 4.1.1
Missing Data Information and Generation: Data Set A (Vital Signs)

DRUG	CENTER	PATIENT	TIMES WHEN MISSING	GENERATED?
1	1	10011	1	Yes
		10034	13	Yes
		10050	18,19	Yes
1	2	20034	23	Yes
2	1	10040	3	Yes
2	2	20022	13	Yes
3	1	10031	23	Yes
		10038	1,2,3	No, Deleted
3	2	20045	14,18,19,20,21,22	No, Deleted
		20039	18,19,20	Yes
4	1	10024	23	Yes
4	2	20021	22,23	Yes
1	2	20048	0	No, Retained
2	1	10033	0	No, Retained

NOTE: Each individual had missing data for all three vital signs heart rate, systolic and diastolic BP.

Table 4.1.2
Missing Data and Generation Infor mation: Data Set B (Dietary Response)

THERAPY	SUBJECT	TIMES WHEN MISSING	GENERATED?
GROUP 1	3	6	Yes
GROUP 2	16	3, 4	No, Deleted
GROUP 3	18	8	Yes
	22	9	No, Deleted

4.2.2: Ad-hoc Data Generation Method

Since the main purpose of this thesis was not to deal with missing data but was to look at approaches and problems related to the approaches used, it was decided to regenerate the missing data using the ad-hoc method devised for the data sets specific to this thesis. It must be noted that this may not be appropriate for all data sets and may need to be modified according to the data being looked at. The method was as follows:

Initially any patients that fell into the following three categories were deleted:

a) A patient withdrew early or had a missing last observation.

b) A patient's records did not begin until after time 2.

c) When there was more than 15% missing data within an individual profile.

The following synario was then applied to generate missing data.

1. If the first observation was missing, then the second record was carried back to the first record.

2. If an individual had one missing record, then the two surrounding observations were averaged and this value was used.

3. If two consecutive values were missing then the value on the left was bought forward for one value and the value on the right was bought backward for the next missing value.

4. If an even number of values were missing, then this number was divided by two and that many observations were bought forward and bought backwards.

5. If an odd number of values were missing, then a combination of the two approaches was used. The value 1 was subtracted from the number of missing records. The same approach as point 4 above was applied to the data. This resulted in one missing record, which was imputed using point 2 above.

4.2.3: Generating Missing Data

Some of the missing data were generated using the ad-hoc method stated in section 4.2.2 above. The individuals for whom data were or were not generated are highlighted on Tables 4.1.1 and 4.1.2 above. From the process described, the on-treatment-missing records were not generated for 2 individuals within both data sets A and B. Hence, following the ad-hoc data generation process, data set A had 84 complete on-treatment records and had two missing baseline records and data set B had 22 complete on-treatment records. Permanent univariate and multivariate data sets were produced on the data after data generation as were produced for the original data format. The univariate data sets were called 'UNI_2' and the multivariate data sets were called 'MULT_2'.

4.3 Distribution of the Continuous Data Over Time

Box-plots were produced below for each treatment for both data set A (Figures 4.2.1 to 4.2.3) and B (Figure 4.2.4). In each case, similar patterns to those for the profile plots were observed. The box plots each displayed the median, minimum, maximum and quintiles of the data at each univariate time point per treatment group. The data did not appear to have a normal distribution at each univariate time point per treatment group. Hence, a non-parametric Kruskal-Wallis approach was taken to test between treatment groups at each univariate time point. Tables of summary statistics for these plots were produced for the original data (Tables 1a-1d, Appendix A) and data sets after imputing the missing information (Tables 2a-2d, Appendix A). The respective summary statistics in Tables 1a-1d are those values displayed in the box-plots below (Figures 4.2.1-4.2.4). Univariate (Normality and non-parametric Kruskal-Wallis) tests were conducted on the data and the test results are also displayed. The hypothesis for the univariate normal test was as follows:

H_0: The data is normally distributed. H_1: The data is non-normal.

This was obtained using the following code in SAS:

```
PROC UNIVARIATE NORMAL;
   VAR VALUE;
    BY DRUG TIME; **DATA SET A, CHANGE DRUG TO GROUP FOR DATA SET B ***;
RUN;
```

The hypothesis for the univariate Wilcoxon (for n=2 groups) or Kruskal-Wallis (for n > 2 groups) tests was as follows: H_0: There is no difference in treatment.

H_1: There is significant evidence to suggest a treatment difference.

This was obtained using the following code in SAS:

```
PROC NPAR1WAY WILCOXON;
   CLASS TIME;
   VAR VALUE;
    BY TIME; **DATA SET A, CHANGE DRUG TO GROUP FOR DATA SET B ***;
RUN;
```

These tests were conducted on both forms of data in order to see whether there were any vast differences in testing the data univariately after imputing missing data records. Comparisons of test results before and after imputing missing data are displayed in Tables 4.2.1-4.2.4 below. Notice that in the case of the univariate tests, the results both before and after imputing data are almost identical. As mentioned above, the only purpose of analysing times in a univariate manner was to note differences in results obtained from the data sets before and after data replacement. There were also far too many univariate tests being conducted and not all groups were normal for all cases. Hence it was decided that parametric

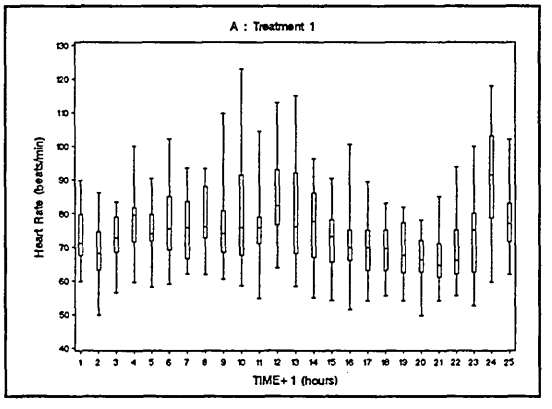
test procedures based on asymptotic theory (reducing the number p of repeated measures) or non-parametric tests approaches would be a more appropriate way of handling this data rather than transforming the data for multivariate analyses purposes.

4.3.1: Heart Rate

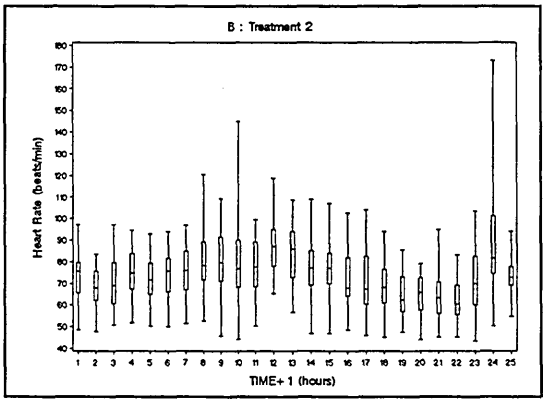
Box-plots of summary statistics for Heart Rate (beats/minute) by treatment groups are displayed in Figures 4.2.1 A-D below.

FIGURE 4.2.1
Box Plot of Distribution of Heart Rate (beats/min) over Time by Treatment Group. Original Data: Before Missing Data Replaced (N=86).

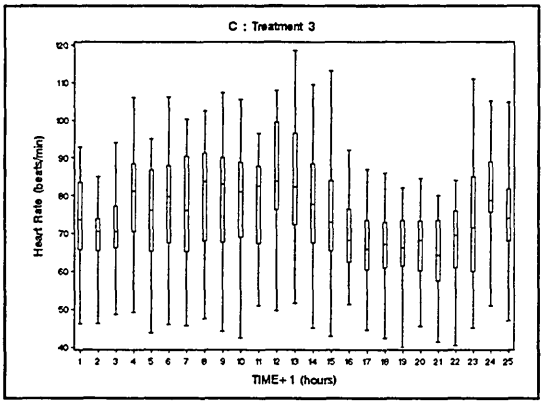
A : Treatment 1



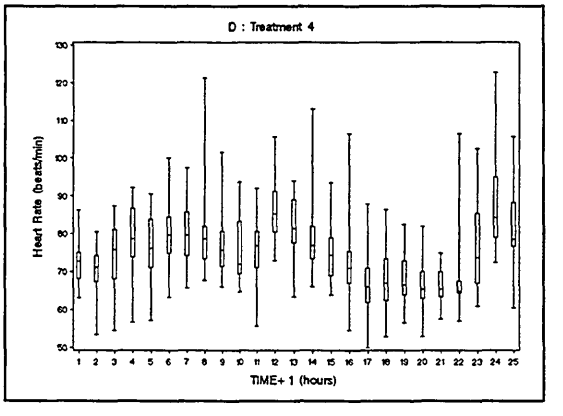
B : Treatment 2



C : Treatment 3



D : Treatment 4



Summary statistics with tests for normality at each time point are displayed in Table 1a (Appendix A). Table 2a (Appendix A) shows this same table for data after imputing missing records. From the tests of normality in Table 4.2.1 below, it can be seen that the original data is not normally distributed for drug 1 at time 15 hours, drug 2 at times 9 and 23 hours and drug 4 at times 7, 8, 9, 13, 15, 21 and 23 hours. All other data time points are normally distributed. These results are identical for the data after imputing missing data. In testing for treatment differences at each time point, using non-parametric Kruskal-Wallis tests, it was found that there were no treatment differences in the data for both the original data and the data after imputing missing data.

Table 4.2.1
Normal Tests Per Treatment and Non-Parametric Treatment Difference Tests Over Time
P-Values to Compare Before and After Data Generation: Heart Rate (b/m)

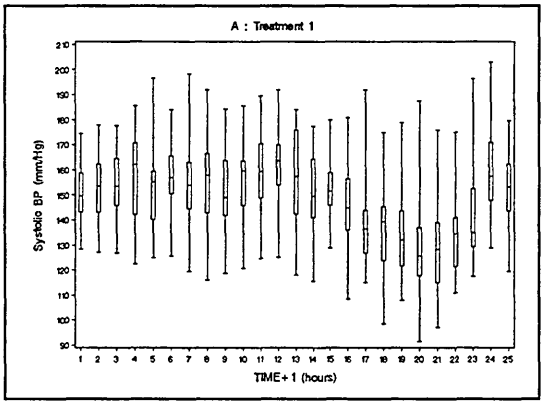
Time	Dataset	Normal Tests For Each Treatment Group				K-Wallis
		1	2	3	4	
Baseline	Before	0.288	0.354	0.531	0.348	0.918
0	After	0.288	0.354	0.280	0.348	0.921
1	Before	0.731	0.762	0.357	0.179	0.906
	After	0.749	0.762	0.356	0.179	0.871
2	Before	0.632	0.422	0.531	0.088	0.554
	After	0.632	0.422	0.473	0.088	0.543
3	Before	0.402	0.829	0.661	0.144	0.528
	After	0.402	0.736	0.497	0.144	0.609
4	Before	0.578	0.936	0.197	0.863	0.554
	After	0.578	0.936	0.200	0.863	0.558
5	Before	0.632	0.845	0.973	0.977	0.486
	After	0.632	0.845	0.892	0.977	0.508
6	Before	0.238	0.959	0.506	0.897	0.631
	After	0.238	0.959	0.628	0.897	0.646
7	Before	0.245	0.177	0.123	**<0.001***	0.913
	After	0.245	0.177	0.113	**<0.001***	0.919
8	Before	0.089	0.734	0.535	**0.029***	0.693
	After	0.089	0.734	0.461	**0.029***	0.677
9	Before	0.082	**0.014***	0.505	**0.025***	0.894
	After	0.082	**0.014***	0.554	**0.025***	0.922
10	Before	0.143	0.704	0.098	0.608	0.721
	After	0.143	0.704	0.097	0.608	0.692
11	Before	0.637	0.884	0.152	0.266	0.846
	After	0.637	0.884	0.187	0.266	0.840
12	Before	0.098	0.570	0.751	0.224	0.648
	After	0.098	0.570	0.636	0.224	0.643
13	Before	0.648	0.917	0.958	**<0.001***	0.977
	After	0.516	0.937	0.920	**<0.001***	0.995
14	Before	0.815	0.823	0.827	0.182	0.724
	After	0.815	0.823	0.984	0.182	0.642
15	Before	**0.038***	0.125	0.531	**0.016***	0.866
	After	**0.038***	0.125	0.691	**0.016***	0.825
16	Before	0.901	0.490	0.747	0.108	0.843
	After	0.901	0.490	0.777	0.108	0.827
17	Before	0.946	0.903	0.690	0.655	0.868
	After	0.946	0.903	0.540	0.655	0.848
18	Before	0.475	0.704	0.341	0.862	0.431
	After	0.506	0.704	0.330	0.862	0.427
19	Before	0.639	0.656	0.768	0.724	0.855
	After	0.645	0.656	0.775	0.724	0.850
20	Before	0.390	0.257	0.525	0.671	0.782
	After	0.390	0.257	0.912	0.671	0.784
21	Before	0.082	0.384	0.528	**<0.001***	0.254
	After	0.082	0.984	0.697	**<0.001***	0.269
22	Before	0.568	0.573	0.525	0.112	0.644
	After	0.568	0.573	0.301	0.101	0.524
23	Before	0.939	**0.006***	0.438	**0.024***	0.250
	After	0.947	**0.006***	0.636	**0.036***	0.184
24	Before	0.626	0.299	0.714	0.167	0.141
	After	0.626	0.299	0.510	0.167	0.120

4.3.2: Systolic Blood Pressure (mmHg)

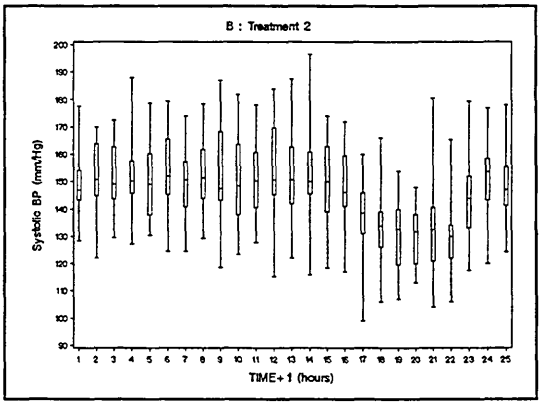
A clearer picture of the behaviour of the data can be observed from the box-plots of the data seen in Figures 4.2.2 A-D below. The data appears to be highly skewed at some of the time points and there is a great deal of variation in the ranges for the data at each time point.

FIGURE 4.2.2
Box Plot of Distribution of Systolic Blood Pressure over Time by Treatment Group.
Original Data: Before Missing Data Replaced (N=86).

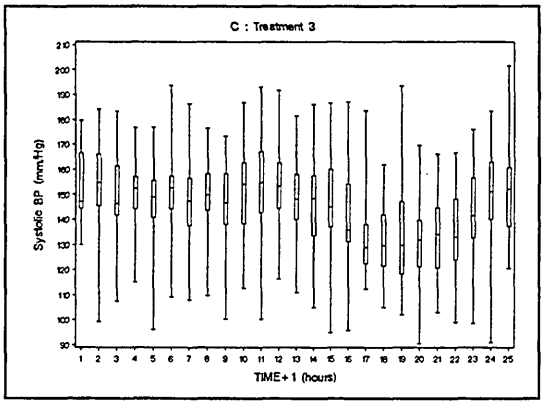
A: Treatment 1



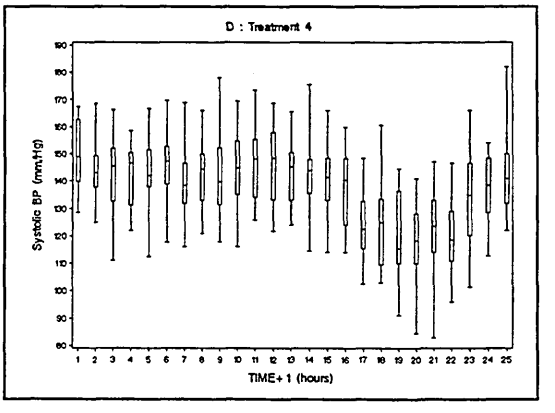
B : Treatment 2



C : Treatment 3



D : Treatment 4



Summary statistics with tests for normality at each time point are displayed in Table 1b (Appendix A). Table 2b (Appendix A) shows this same table for data after imputing missing records. From Table 4.2.2 below, it can be seen that the original data is not normally distributed for drug 1 at times 16 and 22 hours, drug 2 at times 20 and 21 hours, drug 3 at times 0, 16 and 24 hours and drug 4 at 3 hours. All other data time points are normally distributed. These results are almost identical for the data after imputing missing data with the exception of for drug 3 at time 24 hours where the data is marginally normally distributed. In testing for treatment differences at each time point, it was found that there were treatment differences in both the original and imputing data at times 1, 3, 5, 6, 7, 8 16, 17, 18, 19, 21, 23 and 24 hours. Only the non-normal reading (p=0.027) at time 24 hour on drug 3 was later tested to be normally distributed following the data generation method (p=0.054). This inconsistency is not serious.

Table 4.2.2

Normal Tests Per Treatment and Non-Parametric Treatment Difference Tests Over Time

P-Values to Compare Before and After Data Generation: Systolic BP (mmHg)

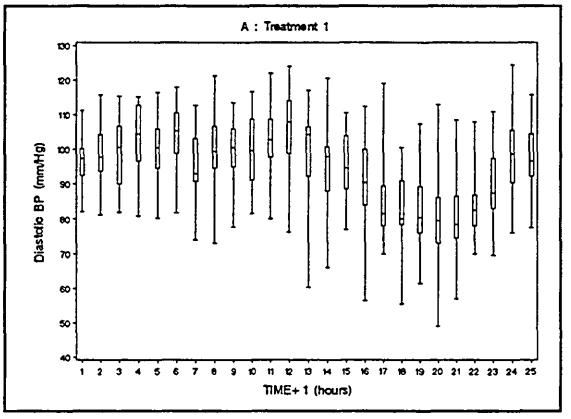
Time	Dataset	Normal Tests For Each Treatment Group				K-Wallis
		1	2	3	4	
Baseline	Before	0.968	0.385	**0.041***	0.066	0.857
0	After	0.968	0.385	**0.029***	0.066	0.866
1	Before	0.794	0.278	0.150	0.808	**0.038***
	After	0.913	0.278	0.110	0.808	**0.022***
2	Before	0.864	0.416	0.425	0.727	0.110
	After	0.864	0.416	0.607	0.727	0.111
3	Before	0.374	0.327	0.624	**0.025***	**0.015***
	After	0.374	0.298	0.369	**0.025***	**0.012***
4	Before	0.633	0.089	0.057	0.426	0.186
	After	0.633	0.089	0.058	0.426	0.186
5	Before	0.947	0.990	0.071	0.922	**0.033***
	After	0.947	0.990	0.141	0.922	**0.035***
6	Before	0.149	0.856	0.901	0.752	**0.005***
	After	0.149	0.856	0.903	0.752	**0.006***
7	Before	0.690	0.985	0.335	0.465	**0.023***
	After	0.690	0.985	0.378	0.465	**0.024***
8	Before	0.483	0.214	0.193	0.502	**0.039***
	After	0.483	0.214	0.201	0.502	**0.042***
9	Before	0.786	0.902	0.963	0.815	0.150
	After	0.786	0.902	0.972	0.815	0.151
10	Before	0.839	0.449	0.506	0.317	0.054
	After	0.839	0.449	0.498	0.317	0.050
11	Before	0.748	0.343	0.986	0.219	0.059
	After	0.748	0.343	0.959	0.219	0.058
12	Before	0.538	0.884	0.711	0.264	0.053
	After	0.538	0.884	0.358	0.264	0.052
13	Before	0.649	0.473	0.996	0.536	0.120
	After	0.715	0.548	0.881	0.536	0.117
14	Before	0.890	0.539	0.421	0.786	0.082
	After	0.890	0.539	0.534	0.786	0.084
15	Before	0.935	0.234	0.782	0.139	0.154
	After	0.935	0.234	0.884	0.139	0.163
16	Before	**0.006***	0.221	**0.002***	0.662	**0.002***
	After	**0.006***	0.221	**0.002***	0.662	**0.002***
17	Before	0.921	0.179	0.690	0.189	**0.037***
	After	0.921	0.179	0.643	0.189	**0.036***
18	Before	0.359	0.492	0.205	0.167	**0.049***
	After	0.574	0.492	0.063	0.167	**0.039***
19	Before	0.056	0.087	0.733	0.838	**0.023***
	After	0.118	0.087	0.916	0.838	**0.033***
20	Before	0.282	**0.016***	0.909	0.379	0.199
	After	0.282	**0.016***	0.840	0.379	0.335
21	Before	0.175	**0.034***	0.514	0.464	**0.016***
	After	0.175	**0.034***	0.651	0.464	**0.020***
22	Before	**0.018***	0.343	0.811	0.922	0.398
	After	**0.018***	0.343	0.452	0.852	0.491
23	Before	0.430	0.242	0.308	0.455	**0.003***
	After	0.388	0.242	0.235	0.719	**0.007***
24	Before	0.982	0.422	**0.027***	0.091	**0.041***
	After	0.982	0.422	0.054	0.091	**0.036***

4.3.3: Diastolic Blood Pressure (mmHg)

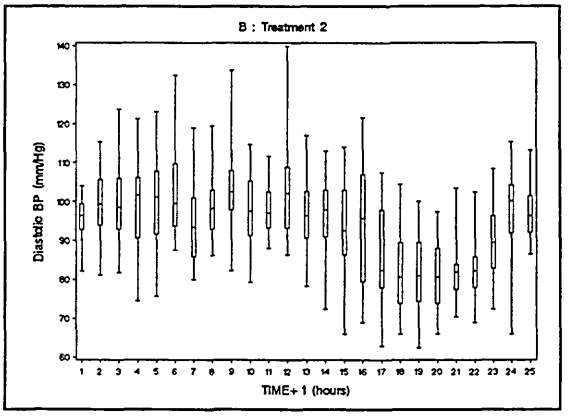
A clearer picture of the data could be obtained from the box-plots of the data below (Figures 4.2.3A-D). The data on drug 3 appeared to have much more variation at each time point than the other treatments.

FIGURE 4.2.3
Box Plot of Distribution of Diastolic Blood Pressure over Time by Treatment Group: Original Data: Before Missing Data Replaced (N=86).

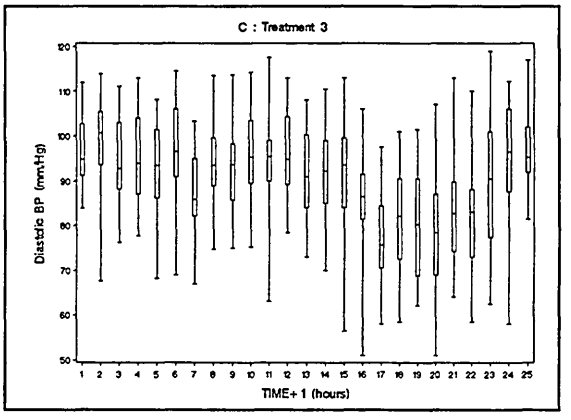
A : Treatment 1



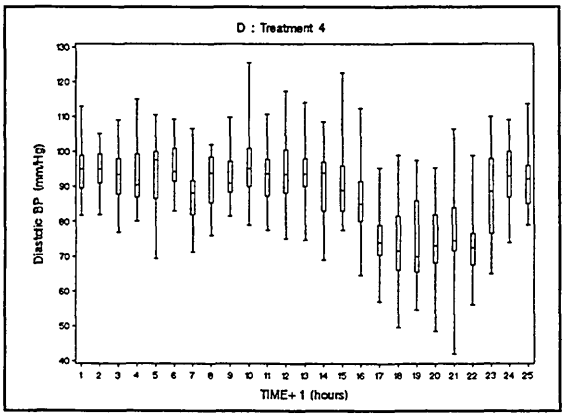
B : Treatment 2



C : Treatment 3



D : Treatment 4



Summary statistics with tests for normality at each time point are displayed in Table 1c (Appendix A). Table 2c (Appendix A) shows this same table for data after imputing missing records. From Table 4.2.3 below, it can be seen that the original data is not normally distributed for drug 1 at times 12 and 16 hours, drug 2 at times 11, 20 and 23 hours, drug 3 at 23 hours and drug 4 at 14 hours. All other data time points are normally distributed. These results are almost identical for the data after imputing missing data with the exception of for drug 3 at time 1, normal reading (p=0.078) on drug 3 was later tested to be non-normally distributed following the data generation method (p=0.045). This inconsistency is nothing to worry about. In testing for treatment differences at each time point, it was found that there were treatment differences in both the original data and the data after imputing missing data at times 3, 5, 6, 7, 8, 10, 11, 16 and 21 hours.

Table 4.2.3

Normal Tests Per Treatment and Non-Parametric Treatment Difference Tests Over Time

P-Values to Compare Before and After Data Generation: Diastolic BP (mmHg)

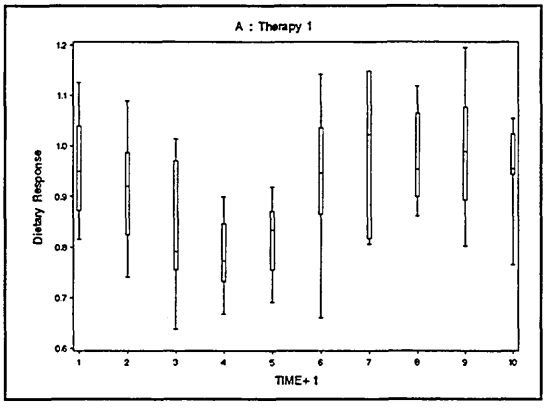
Time	Dataset	Normal Tests For Each Treatment Group				K-Wallis
		1	2	3	4	
Baseline	Before	0.995	0.128	0.528	0.425	0.900
0	After	0.995	0.128	0.663	0.425	0.894
1	Before	0.799	0.964	0.078	0.540	0.173
	After	0.728	0.964	**0.045***	0.540	0.118
2	Before	0.536	0.859	0.689	0.981	0.145
	After	0.536	0.859	0.709	0.981	0.164
3	Before	0.061	0.699	0.378	0.305	**0.019***
	After	0.061	0.658	0.323	0.305	**0.020***
4	Before	0.475	0.992	0.461	0.200	0.062
	After	0.475	0.992	0.525	0.200	0.065
5	Before	0.094	0.068	0.427	0.594	**0.035***
	After	0.094	0.068	0.402	0.594	**0.030***
6	Before	0.497	0.091	0.450	0.695	**0.017***
	After	0.497	0.091	0.641	0.695	**0.016***
7	Before	0.621	0.408	0.721	0.244	**0.019***
	After	0.621	0.408	0.666	0.244	**0.015***
8	Before	0.513	0.227	0.833	0.099	**0.004***
	After	0.513	0.227	0.969	0.099	**0.003***
9	Before	0.664	0.821	0.610	0.446	0.673
	After	0.664	0.821	0.587	0.446	0.633
10	Before	0.503	0.338	0.061	0.545	**0.019***
	After	0.503	0.338	0.076	0.545	**0.019***
11	Before	0.496	**0.045***	0.347	0.743	**0.033***
	After	0.496	**0.045***	0.277	0.743	**0.031***
12	Before	**0.030***	0.299	0.599	0.676	0.204
	After	**0.030***	0.299	0.312	0.676	0.293
13	Before	0.415	0.810	0.366	0.415	0.276
	After	0.267	0.761	0.621	0.415	0.279
14	Before	0.538	0.166	0.166	**0.017***	0.521
	After	0.538	0.166	0.222	**0.017***	0.474
15	Before	0.248	0.602	0.060	0.810	0.095
	After	0.248	0.602	0.197	0.810	0.090
16	Before	**0.011***	0.691	0.809	0.626	**0.006***
	After	**0.011***	0.691	0.695	0.626	**0.008***
17	Before	0.143	0.752	0.831	0.928	0.070
	After	0.143	0.752	0.680	0.928	0.073
18	Before	0.400	0.521	0.320	0.060	0.151
	After	0.295	0.521	0.405	0.060	0.147
19	Before	0.330	0.213	0.962	0.998	0.216
	After	0.225	0.213	0.659	0.998	0.214
20	Before	0.340	**0.025***	0.748	0.244	0.327
	After	0.340	**0.025***	0.701	0.244	0.459
21	Before	0.111	0.480	0.897	0.071	**0.018***
	After	0.111	0.480	0.612	0.071	**0.020***
22	Before	0.294	0.539	0.946	0.656	0.882
	After	0.294	0.539	0.461	0.653	0.810
23	Before	0.660	**0.032***	**0.015***	0.789	0.430
	After	0.666	**0.032***	**0.022***	0.878	0.530
24	Before	0.499	0.472	0.786	0.151	0.156
	After	0.499	0.472	0.902	0.151	0.128

4.3.4: Dietary Response

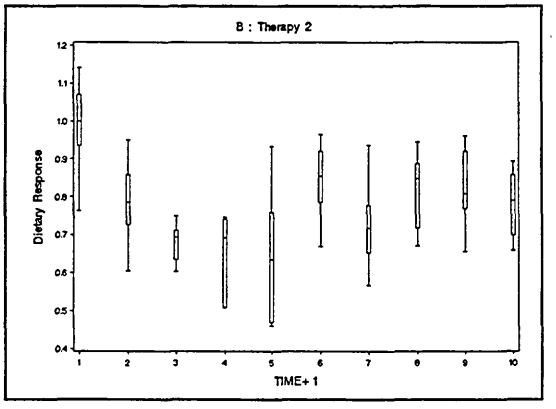
Dietary response can be seen more clearly in the box plots below (Figures 4.2.4 A-C) that show both the variations in the data and also the distribution of the data at each time point. Therapy 3 is a function that is decreasing with time.

FIGURE 4.2.4
Boxplot of Distribution of Dietary Response over Time (hours) by Therapy group. Original Data: Before Missing Data Replaced (N=24).

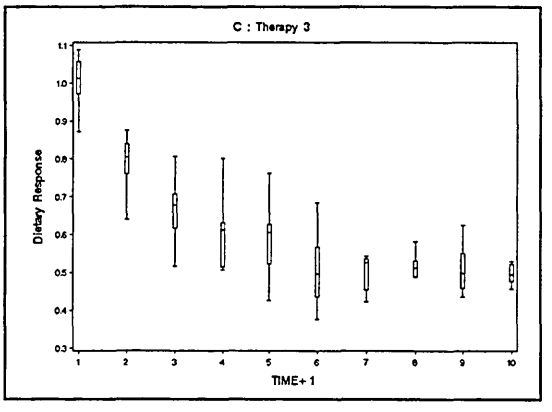
A : Therapy 1



B : Therapy 2



C: Therapy 3



Summary statistics with tests for normality at each time point are displayed in Table 1d (Appendix A). Table 2d (Appendix A) shows this same table for data after imputing missing records. From Table 4.2.4 below, it can be seen that the original data is not normally distributed for therapy 3 at time 6. All other data time points are normally distributed. These results are almost identical for the data after imputing missing data with the exception of for therapy 3 at time 3 where the data are also not normally distributed. In testing for treatment differences at each time point, it was found that there were treatment differences in both the original data and the data after imputing missing data at times 2, 3, 4, 5, 6, 7, 8 and 9. In other words, all times apart from baseline and time 1 were significantly different for therapy groups.

Table 4.2.4

Normal Tests Per Treatment and Non-Parametric Treatment Difference Tests Over Time

P-Values to Compare Before and After Data Generation: Dietary Response

Time	Dataset	Normal Tests For Each Therapy			K-Wallis
		1	2	3	
Baseline 0	Before	0.835	0.744	0.664	0.539
	After	0.835	0.359	0.749	0.495
1	Before	0.952	0.992	0.335	0.077
	After	0.952	0.975	0.562	0.090
2	Before	0.350	0.372	0.887	**0.009***
	After	0.350	0.412	0.835	**0.013***
3	Before	0.795	0.109	0.103	**0.010***
	After	0.795	0.109	**0.028***	**0.004***
4	Before	0.231	0.665	0.815	**0.007***
	After	0.231	0.665	0.557	**0.011***
5	Before	0.866	0.856	0.786	**<0.001***
	After	0.866	0.856	0.782	**<0.001***
6	Before	0.069	0.844	**0.032***	**<0.001***
	After	0.170	0.912	**0.023***	**<0.001***
7	Before	0.277	0.373	0.151	**<0.001***
	After	0.277	0.261	0.127	**<0.001***
8	Before	0.844	0.755	0.729	**<0.001***
	After	0.844	0.961	0.777	**<0.001***
9	Before	0.074	0.399	0.755	**<0.001***
	After	0.074	0.334	0.755	**<0.001***

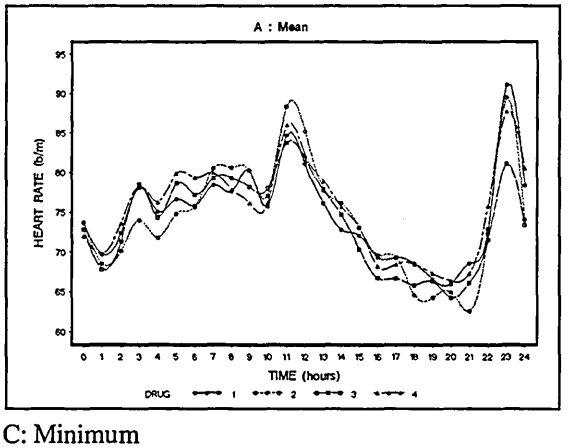
4.4 Plots of Summary Statistic by Treatment over Time

Since it was of interest to see what the mean, median, maximum and minimum profiles looked like, appropriate profile plots were produced to show the differences between treatment or therapy group. Figures 4.3.1-4.3.4 below, show the plots for the respective summary statistics for heart rate, systolic BP, diastolic BP and dietary response respectively and Tables 1a-1d (Appendix A) show the actual summary statistics used in these plots. A commonly used plot of the mean response profile over time together with standard error bars was then produced for each variable in data sets A and B and these are displayed below in Figures 4.4.1-4.4.4 respectively. These plots gives a better idea of the behaviour of the data over time compared with the picture previously provided by the individual profile plots in Figures 4.1.1-4.1.4 above. The median plots (Figures 4.3.1 B -4.3.4 B) show the difference in treatment or therapy at each time point clearly on one figure (corresponding to the Kruskal-Wallis test results from Tables 1a-1d - Appendix A).

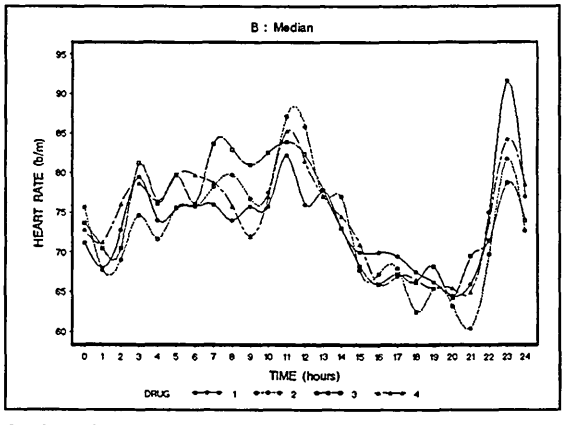
4.4.1: Heart Rate (beats/minute)

FIGURES 4.3.1
Plots of Summary Response Profiles over Time by Treatment GroupFor Heart Rate(b/m): Original Data Before Missing Data Replaced (N=86).

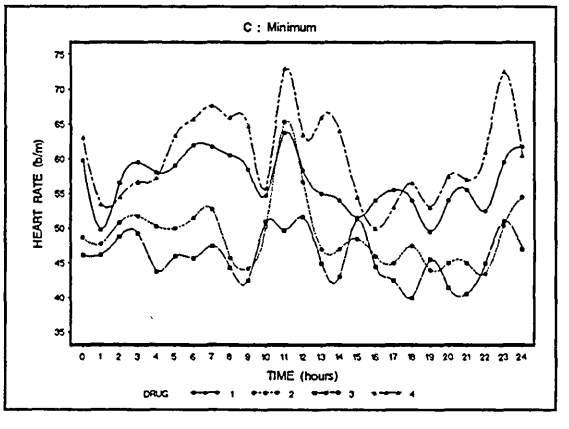
A: Mean



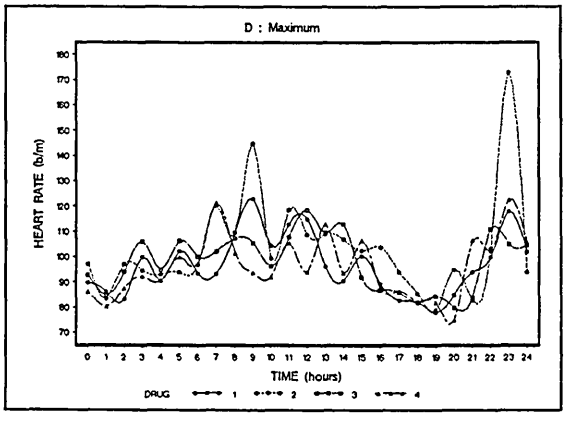
B: Median



C: Minimum



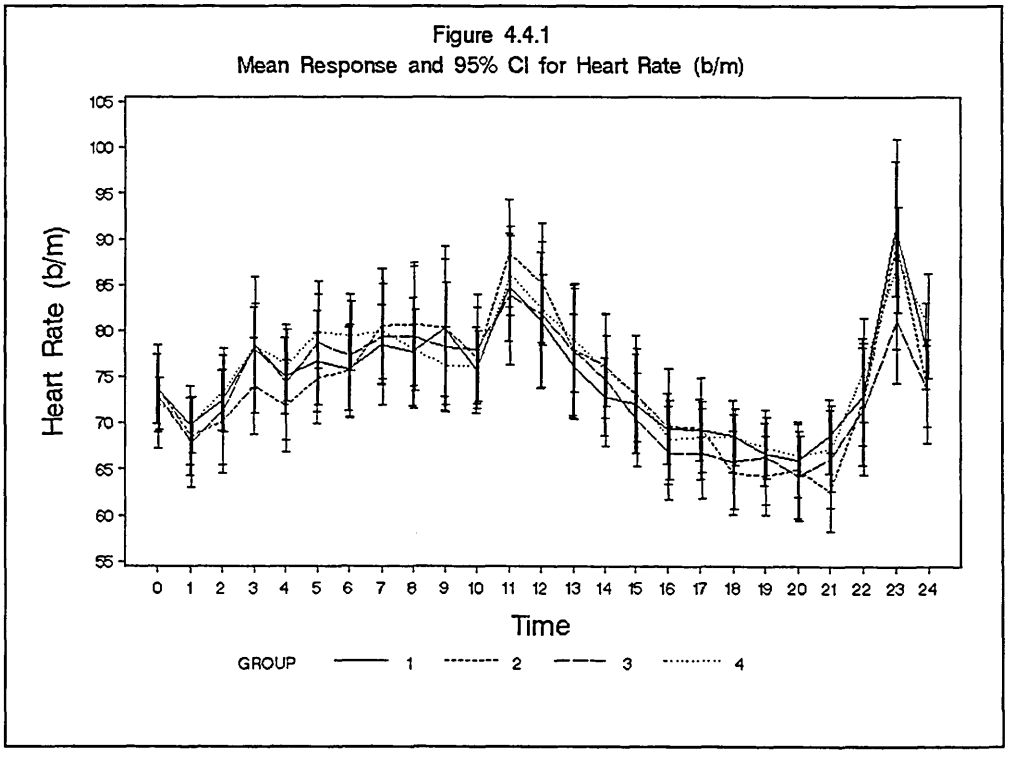
D: Maximum



There were no obvious treatment differences in the mean heart rate over time since the mean responses were very close together (Figure 4.3.1A). The median results (Figure 4.3.1B) appeared to be very similar for all four treatments apart from the fact that there were slightly higher results for drug 3 and lower results for drug 1 at around times 7 to 10 hours on treatment. Drug 1 had considerably larger median levels than the other treatment groups at time 23. Both the minimum and maximum plots over time (Figures 4.3.1C and 4.3.1D respectively) varied randomly after ignoring the two outlying readings at time 11 and 23 for the minimum plot and at times 9 and 23 on the maximum plot. All figures mentioned above gave some idea of the behaviour of the data over time.

From the mean and standard error plot in Figure 4.4.1 below, it can be seen that all standard error bars crossed indicating no significant differences between readings from one time point to the next. The average data peaked at two times, namely at 11 and 23 hours on-treatment.

FIGURE 4.4.1
Mean and Standard Error Plot for Original Heart Rate Data (beats/min) Over Time By Treatment Before Missing Data Replaced.

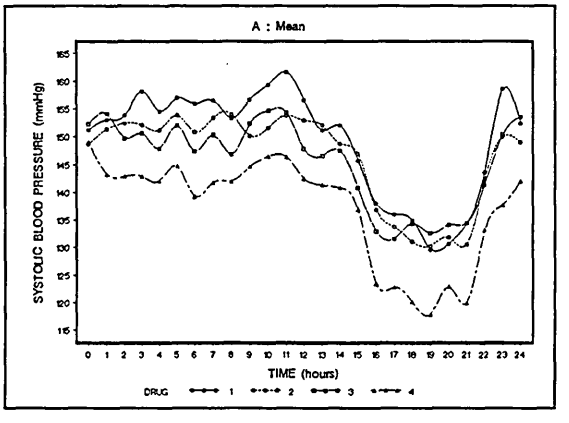


4.4.2: Systolic Blood Pressure (mmHg)

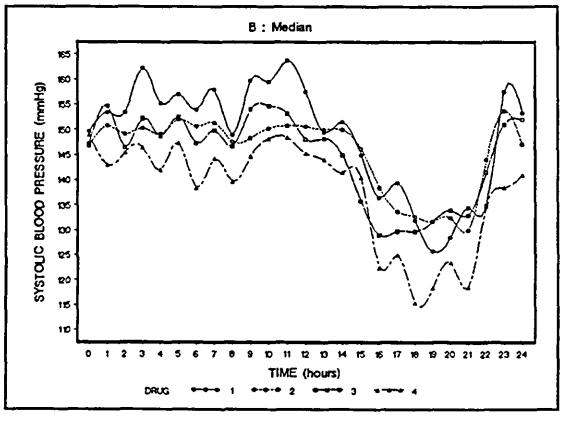
From observing the mean and median plots over time (Figures 4.3.2A and 4.3.2B) it can be seen that the mean data stays pretty constant over time until around 14 hours where it suddenly drops. It then levels off at between 16 to 21 hours after which time it increases to peak at time 23 hours. For the median data, similar patterns exist in the data but there are far more fluctuations between each of the individual time points. Both the minimum and maximum response (Figures 4.3.2C and 4.3.2D) vary considerably over time between each individual time point. There is no obvious pattern to the data apart from the dip in the data around time 14 hours and peak around 23 hours. It can be seen that drug 4 has the lowest mean, median and maximum response overall and after 17 hours the minimum response is also lowest for drug 4. Drug 1 has the highest mean and median response at most of the observed time points.

FIGURES 4.3.2
Plots of Summary Response Profiles over Time by Treatment Group for Systolic BP (mmHg) Original Data Before Missing Data Replaced (N=86).

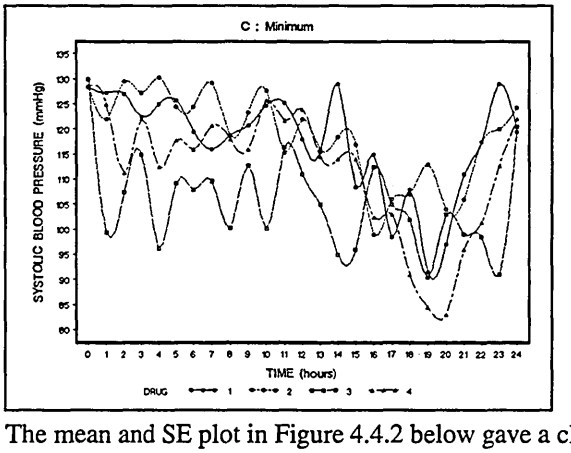
A: Mean



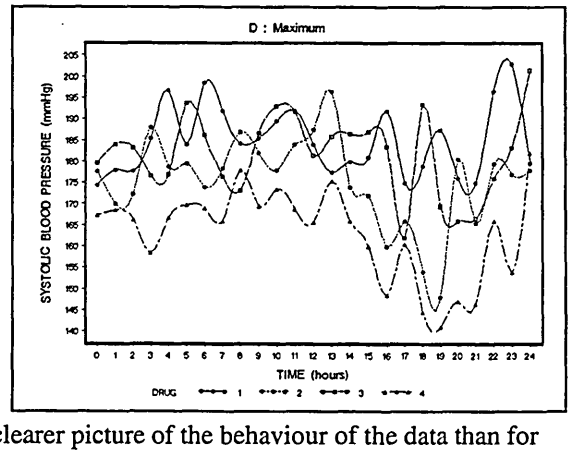
B: Median



C: Minimum



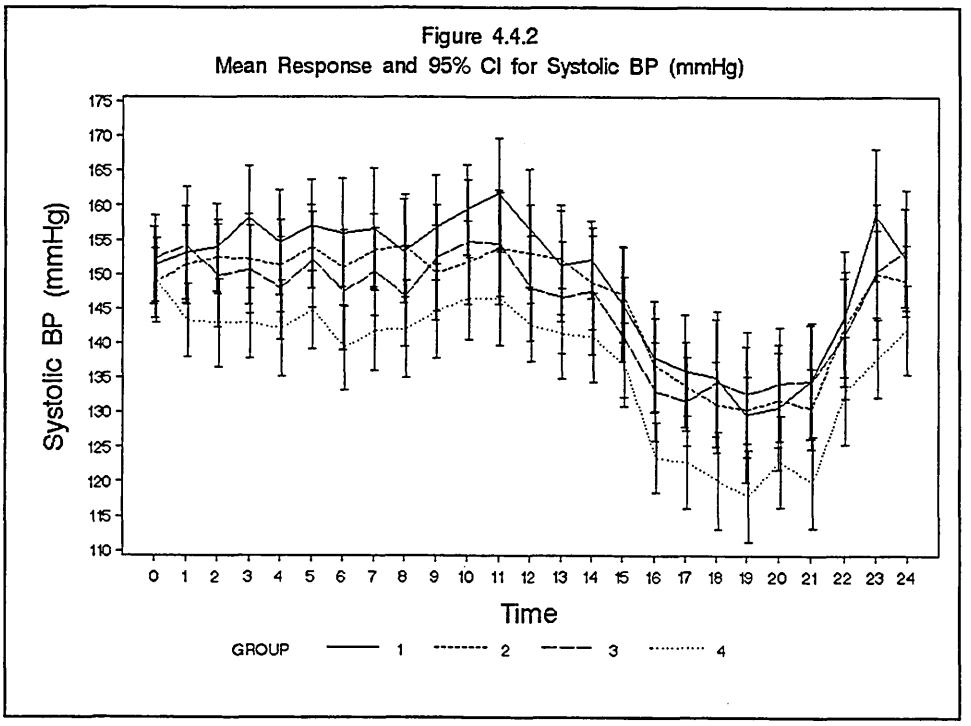
D: Maximum



The mean and SE plot in Figure 4.4.2 below gave a clearer picture of the behaviour of the data than for the individual profile plots (Figure 4.1.2 above). Drug 4 appeared to have lower mean systolic BP than all other treatment groups. The average systolic blood pressure data has two peaks at times 11 and 23 hours respectively.

FIGURE 4.4.2

Mean and Standard Error Plot for Original Systolic Blood Pressure (mmHg) Over Time By Treatment Before Missing Data Replaced.

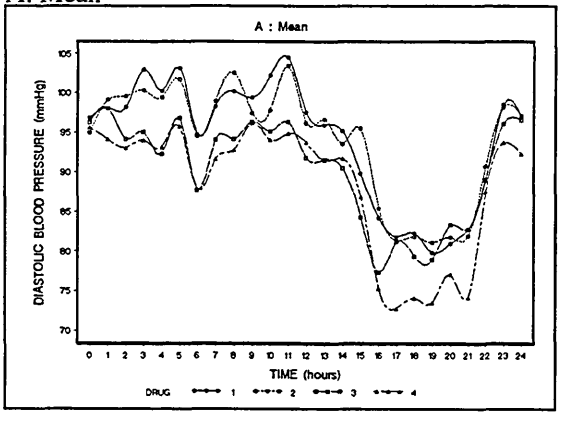


4.4.3: Diastolic Blood Pressure (mmHg)

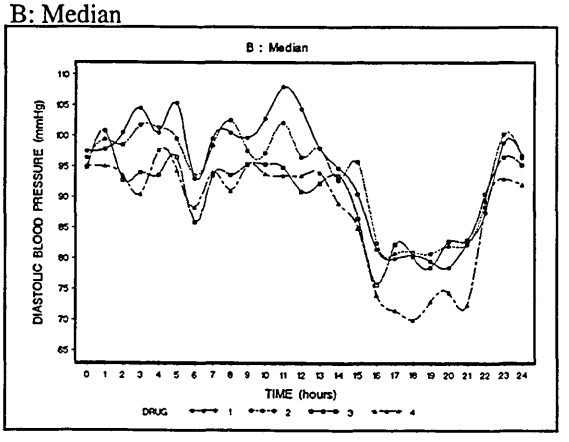
FIGURES 4.3.3

Plots of Summary Response Profiles over Time by Treatment Group for Diastolic BP (mmHg) Original Data Before Missing Data Replaced (N=86).

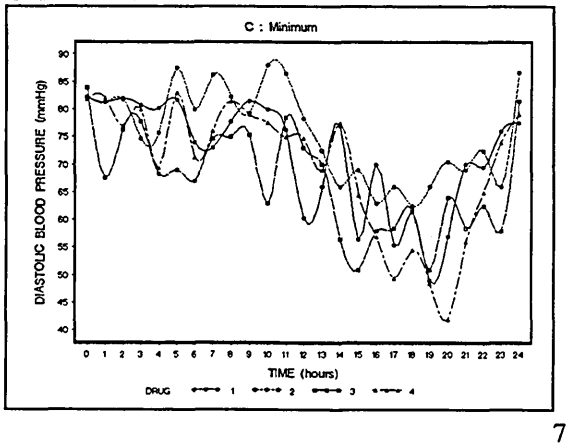
A: Mean



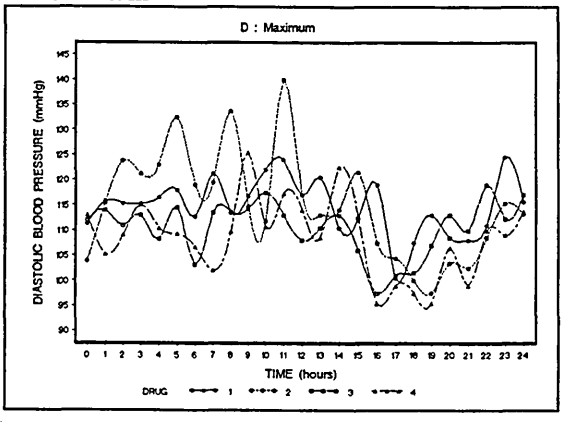
B: Median



C: Minimum



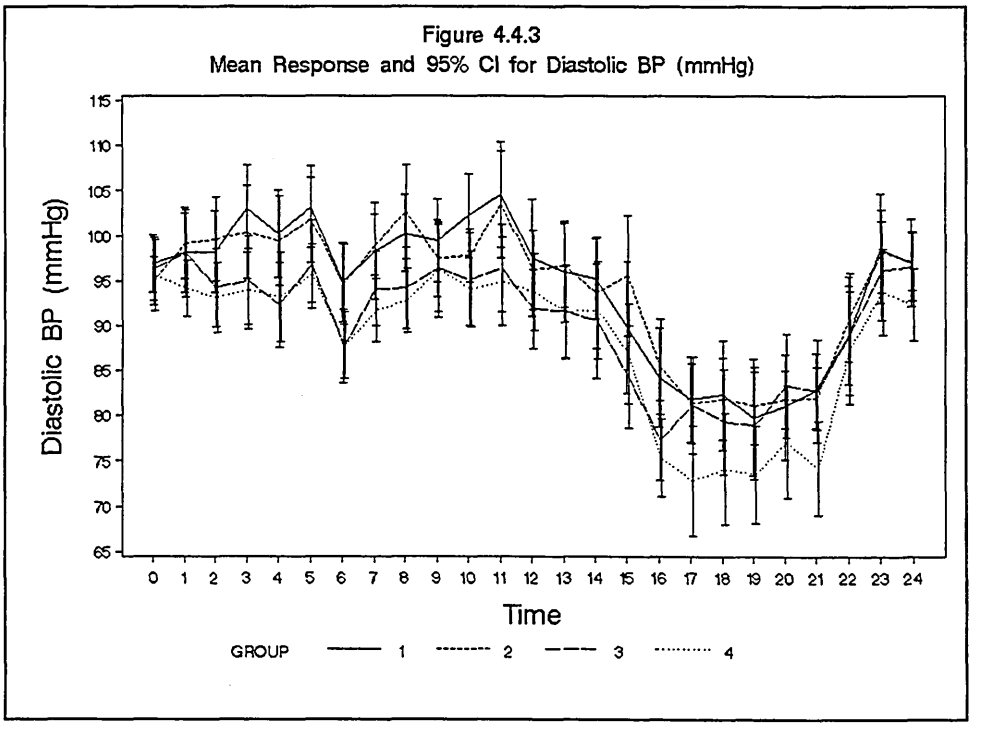
D: Maximum



From observing the mean and median plots over time (Figures 4.3.3A and 4.3.3B) it could be seen that they had similar patterns over time. The mean and median data was constant over time until around 6 hours where it suddenly dropped slightly and then increased again at time 7 hours. The data peaked at 11 hours and then gradually decreased until a plateau was reached from time 16 to 21. After this time the readings increased until they peaked at 23 hours and then began to decrease.

Both the minimum and maximum response (Figures 4.3.3C and 4.3.3D) over time varied considerably between each individual time point and there was no obvious pattern to the data apart from a dip at around 19 hours. It could be seen that drug 4 had the lowest mean, median, minimum and maximum response after 16 hours. The average data seemed almost constant over time until time 6 hours where it dropped slightly. The average readings decreased considerably between 12 to 23 hours (Figure 4.4.3).

FIGURE 4.4.3
Mean and Standard Error Plot for Original Diastolic Blood Pressure (mmHg) Over Time By Treatment Before Missing Data Replaced.

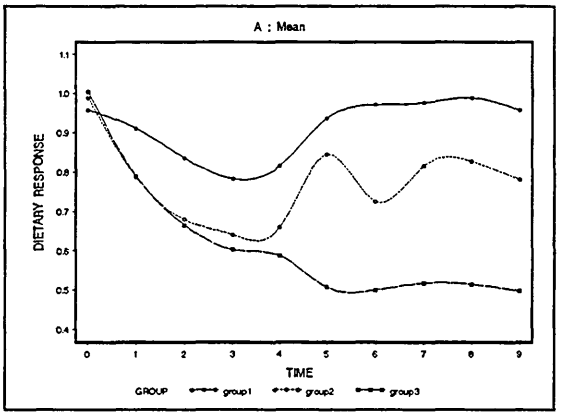


4.4.4: Dietary Response

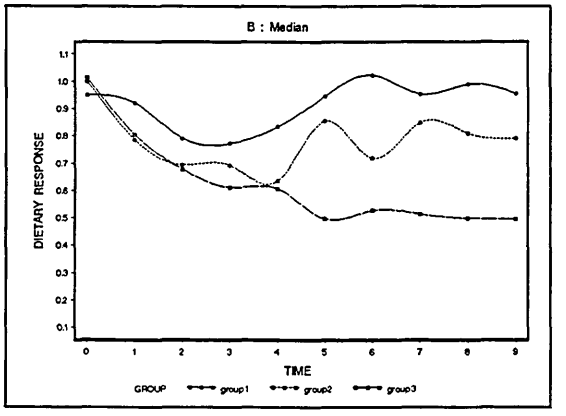
The median plot in Figure 4.3.4B is similar to the mean plot in Figure 4.3.4A. The median response for group 2 varies slightly more than the mean response. The minimum and maximum responses over time are displayed in Figures 4.3.4C and 4.3.4D. The minimum plot is similar in appearance to the median plot. The mean and SE plot (Figure 4.4.4 below) shows that therapy 1 has a much larger mean response over time that the other two groups. Therapy 3 has the lowest mean response for all on treatment time points.

FIGURES 4.3.4
Plots of Summary Response Profiles over Time by Treatment Group for Dietary Data Original Data Before Missing Data Replaced (N=86).

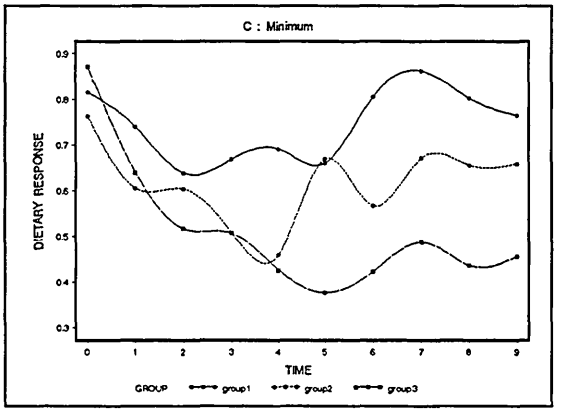
A: Mean



B: Median



C: Minimum



D: Maximum

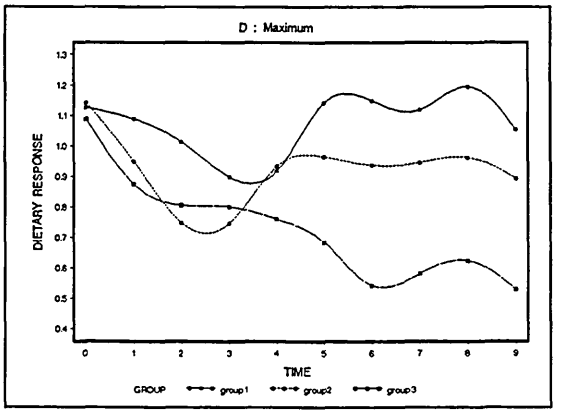
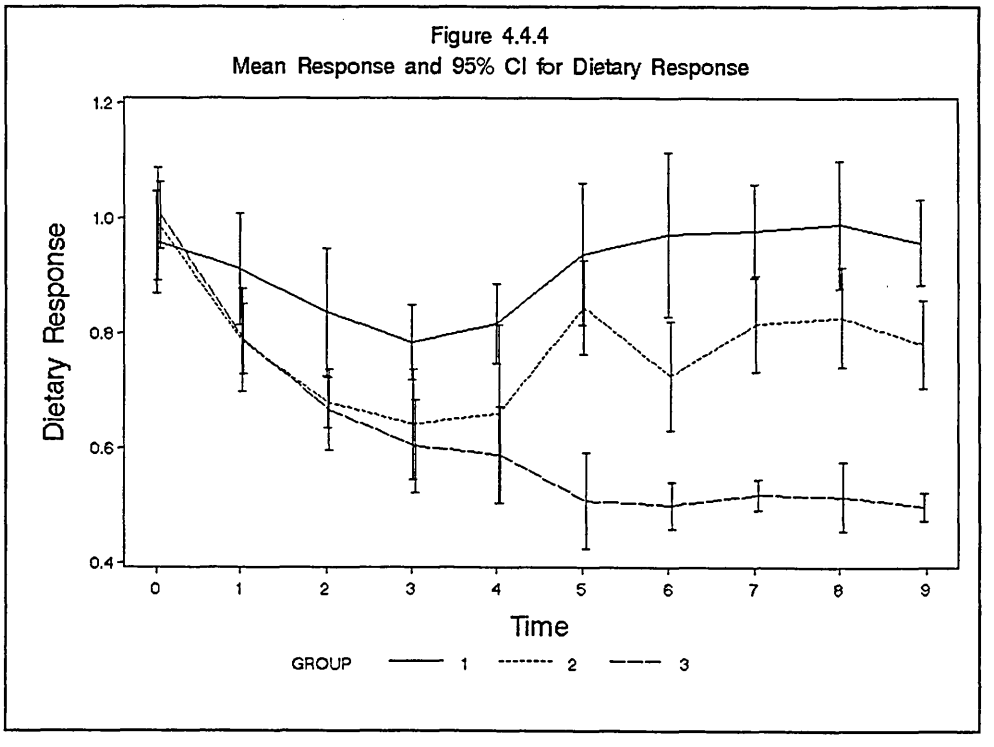


FIGURE 4.4.4
Mean and Standard Error Plot for Original Dietary Data Over Time By Treatment Before Missing Data Replaced.

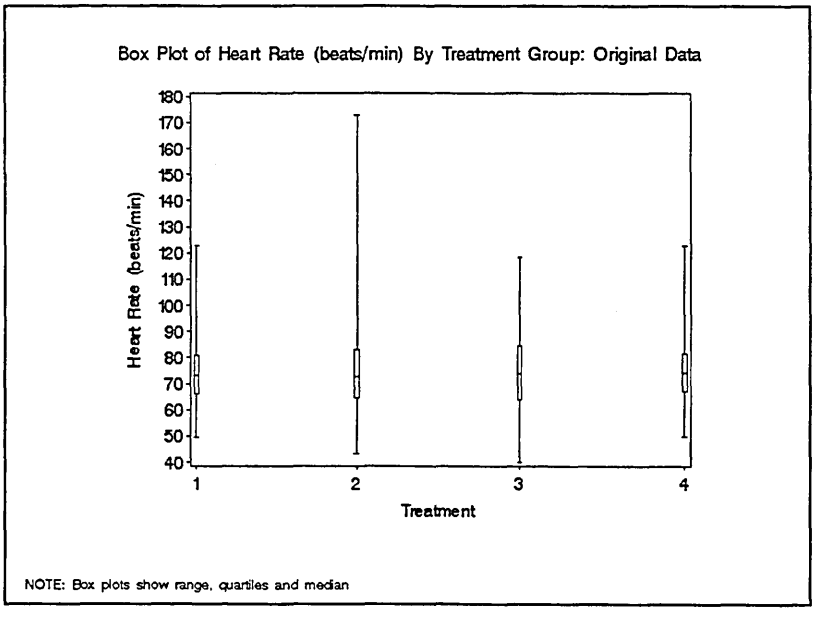


4.5 Distribution of Continuous Overall Data Per Group

Box-plots were produced for each outcome variable by treatment/therapy, assuming that there was independence between every measurement for each subject. In other words, the repeated data per individual were not considered. Hence, time was not considered here and it was therefore assumed that the p=1 to 24 univariate time points per individual were p separate individuals. The plots both before and after data replacement were similar and hence only plots before replacement are displayed below. Note that the only reason for taking this approach was as a rough visualisation guide to find out how the overall data was behaving when the factors of time, centre, baseline measurement and subject were ignored. Further statistical methods were not conducted using this approach.

4.5.1: Heart Rate (beats/minute)

FIGURE 4.5.1

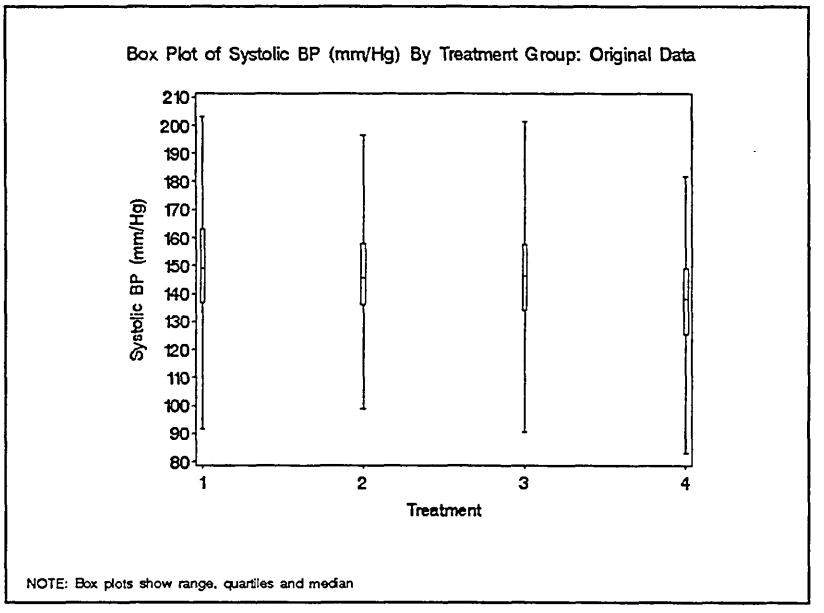


From the box-plot, Figure 4.5.1 above, the median data appear to be similar for all four treatment groups. Drug 2 appears to have the greatest variation in heart rate measurements. The highest overall heart rate measurement occurred on drug 2.

4.5.2: Systolic Blood Pressure (mmHg)

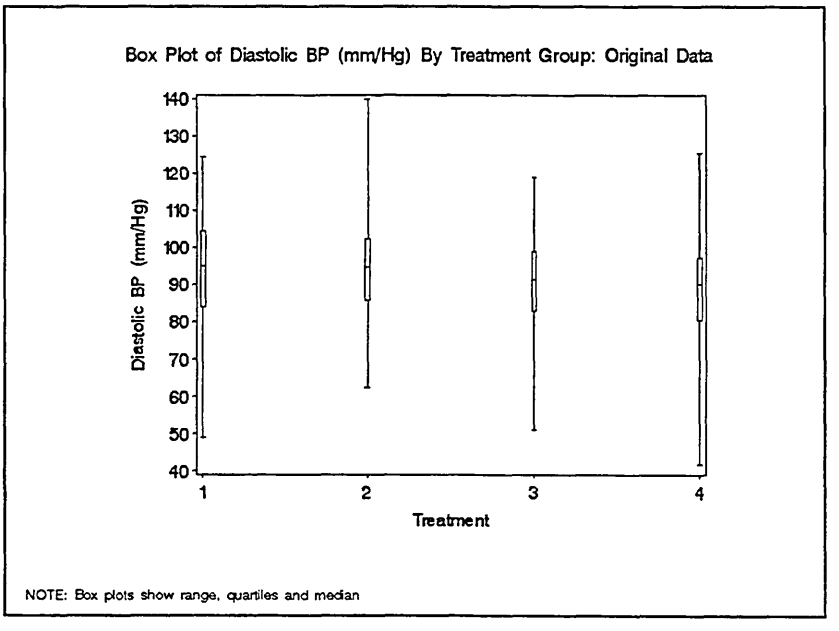
From the box-plot, Figure 4.5.2 below, the median systolic BP on drug 1 seems slightly higher than on any other drug and the median systolic BP on drug 4 seems slightly lower on any other drug. The lowest overall response for systolic blood pressure occurs on drug 4.

FIGURE 4.5.2



4.5.3: Diastolic Blood Pressure (mmHg)

FIGURE 4.5.3

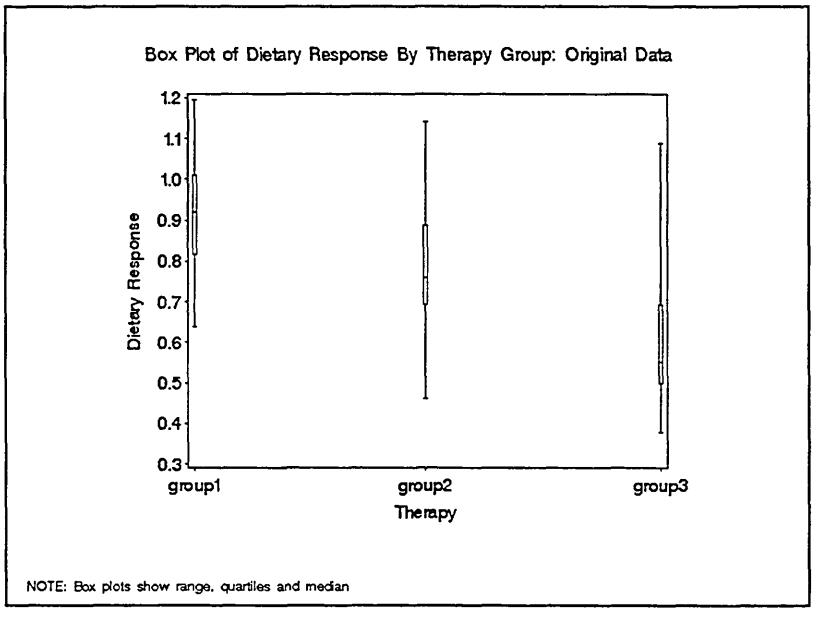


From the box-plot, Figure 4.5.3 above, the median results on drugs 3 and 4 appear to be lower than the median results on drugs 1 and 2. Drug 4 appears to have the greatest variation in diastolic blood pressure readings and also appears to contain the lowest overall response. Drug 2 contains the largest response.

4.5.4: Dietary Response

From the box-plot, Figure 4.5.4 below, the median response is largest for therapy 1 and lowest for therapy 3. Therapy 3 also appears to have a skewed distribution.

FIGURE 4.5.4



4.6 Categorical Approach: Frequency of Abnormally High Results At Each Time.

A categorical approach was only applied to data set A. All data was classified into one of 7 categories according to Table 3.1.1 [section 3.2]. Since there were far too many categories to be able to distinguish clearly between groups, the data was further categorised into three levels of high, low or normal (Table 3.1.2 [section 3.2]) for heart rate, systolic and diastolic BP respectively. Listing 3.3 [section 3.2] provides the structure of this data set. Only the 'high' results were considered to be abnormal and these data were then analysed.

A frequency table of the number of abnormally 'high' results at each time point per treatment group was produced for each variable. The results are displayed in Tables 12a-12c (Appendix A) for the three respective variables (heart rate, systolic and diastolic blood pressure) being analysed. Univariate tests were conducted to test for treatment differences for the number of high results at each univariate time point. Chi-squared tests and when inappropriate (if the expected cell count was less than 5%) Fishers exact tests were conducted to test for the relationship between the abnormal readings at each time point with treatment. All p-values are also displayed in Tables 12a to 12c (Appendix A).

As with the continuous data analysis approach, the method of analysing the data at each univariate time point is not of much use for the same reasons. The main reason against using the univariate time point approach is that having a difference at a particular time point does not explain the picture of the data as a whole. This analysis was conducted as a means of describing the data only.

4.6.1: Heart Rate (beats/minute)

No significant treatment differences were detected at any time point for the occurrence of abnormally 'high' heart rates ($p>0.119$). See Table 12a (Appendix A). These findings correspond to those from all the previous analyses in this chapter. Namely from the Kruskal-Wallis test at each univariate time point. The frequency of individuals with abnormally 'high' heart rate results was very low per treatment group at each time point. There were no occurrences of abnormally 'high' results at times 0, 1, 2, 4, 17, 18, 19 and 20 and there were no more than 7 individuals with an abnormality at any single time point (time 23).

4.6.2: Systolic Blood Pressure (mmHg):

See Table 12b (Appendix A) for the frequency of occurrence of abnormally 'high' results and the Chi-squared test results per time point. Significant treatment differences were detected at 6, 8, 16 and 23 hours ($p<0.019$) for the occurrence of abnormally 'high' systolic BP readings. Differences at all these time points were also found using the univariate Kruskal-Wallis tests that were conducted on the data. In all cases, drug 4 had lower occurrence of 'high' results than the other treatment group. At earlier times, 6 and 8 hours, drug 1 had greater frequency of abnormality and at later times, 16 and 23 hours, drug 2 had higher abnormality. In each case drug 4 had lower readings than the other drugs being studied.

4.6.3: Diastolic Blood Pressure (mmHg)

Table 12c (Appendix A) gives the frequency of abnormally 'high' results and Chi-squared test results. Significant treatment differences were detected at only 6 hours ($p=0.004$) for the occurrence of abnormally 'high' diastolic BP readings. A treatment difference was also picked up at time 6 hours for the median response using the Kruskal-Wallis test. Drug 1 had greater frequency of occurrence of abnormally 'high' readings and drug 3 had fewer occurrences than any other treatment at time 6 hours.

4.7 Overview

All plots in sections 4.1, 4.3 and 4.4 were produced to get a clear idea of the behaviour of the data at both baseline (pre-treatment) and at each individual (on-treatment) time point. Univariate profile plots are not very useful in summarising the data and hence, univariate box-plots or summary measures over time are considered to be the best way of displaying and summarising the data points.

From the box-plots over time (Figures 4.2.1-4.2.4 [section 4.2]) and univariate normal tests (Tables 4.2.1 to 4.2.4 [section 4.2] and Tables 1a-1d (Appendix A)) it can be seen, for all the variables being investigated, that there was not always a consistency in the distribution of the data across time. For this reason, it was decided to use asymptotic or non-parametric approaches to analyse the data when testing for treatment differences at each time point. Most of the time points of data per treatment group or therapy, however, were normally distributed according to the box-plots and normality tests. This statement can be confirmed by looking at the similarity of the mean and median plots over time. Testing for treatment differences per time point is not of any use since the data is not described as a whole element. This type of univariate data analysis is only useful for getting an idea of the behaviour of the data across time. Here, the only purpose for comparing treatment/therapy groups at each univariate time point (Kruskal-Wallis tests), was to be able to compare the data both before and after imputing missing records. The actual results of the tests were not of much importance in this situation.

It was found that the data before and after imputing missing data gave basically similar results for both the normality tests, the tests of comparing treatment groups and also the plots of summary statistics, box-plots and profile plots over time. Hence, in conclusion, imputing missing data does not seriously affect the univariate testing of the data.

When the element of time was not considered [section 4.5] and all observations were presented together as independent records, the plots of the original data and the imputed data were very similar and therefore only the box-plots on the original data are displayed. The method of observing the data without considering the element of time, however, is not reliable since results over time for an individual are not infact independent. This approach was only useful in gaining a feel for the behaviour of the data but, not for making any firm conclusions. Statistical tests were not conducted using this approach.

In conclusion, there were no significant treatment differences at any time point or overall data for the occurrence of an abnormally 'high' heart rate reading. Drug 4 had lower systolic blood pressure than

any other therapy. The only detection of abnormality differences for diastolic blood pressure were noted at time 6 hours where drug 3 had lower readings and drug 1 had highest readings. The following chapter introduces the univariate summary measures, as were introduced in chapter 3.3, to make data inferences.

CHAPTER 5: Univariate Summary Measures Analysis

5.0 Introduction

The previous chapter provided the exploratory data analysis on the data with plots displaying the data for each treatment/therapy at each univariate time point. The normality tests conducted showed that the data was approximately normally distributed at each univariate time point though this does not imply multivariate normality [section 2.1]. It could also be seen that the mean and median plots were very similar over time – confirming this previous point.

Univariate testing at each time point was not of any interest while testing for group differences. The only reason for testing at each time point was to compare the information before and after imputing missing records. Univariate tests over time were not affected by imputing missing data, so only the information for the original data were displayed in the plots in the previous chapter.

The present chapter is concerned with univariate testing of the data after eliminating the association of time. This is done by obtaining various univariate summary measures from the data and analysing each summary measure independently. Each univariate summary measure independently describes the characteristic of the data per individual. This approach is known as a 'Response Features Analysis' or 'Summary Measures Approach'. Of all unvariate approaches considered, this is believed to be the only univariate testing of some substance. Figures and summaries were obtained on both the original data and the data after imputing missing records. Again, as with the plots in the previous chapter, the figures on the imputed data were very similar to those from the original data set so they were not displayed within this chapter.

5.1 Continuous Data Analysis: Response Features Analysis

Every patient had a single measurement for each of the summary statistics (mean, median, minimum, maximum, lower quartile (Q1), upper quartile (Q3), base and change), mentioned in more detail below, for each outcome variable (HR, SBP, DBP and dietary response) of interest. See Listings 3.4.1 and 3.4.2 [section 3.3] for the data structures of summary measures for data sets A and B respectively. Time was no longer a factor during this analysis.

The 8 summary measures above can be described as follows:

1) MEAN, MEDIAN, Minimum (MIN), Maximum (MAX), Lower and Upper Quartiles (Q1 and Q3).

Each of the 6 summary statistics above were calculated over all data for each individual, so that they had just one overall reading of each of the summary statistics above for each outcome variable of interest. Missing data was not a problem for this method since the summary measurements ignored the missing data and calculated measurements on only the available data.

2) Baseline/ Pre-treatment readings (BASE).

The baseline (time=0) or mean run-in reading 'BASE' was assumed to be pre-treatment. Each patient had one measurement for this variable. Data set A had 2 missing baseline records that were never generated and data set B had no missing baseline records.

3) The mean change from baseline.

This was calculated using the difference between the mean response 'MEAN' and also the mean pre-treatment response 'BASE' above.

Univariate normality tests (by treatment / therapy group) and Kruskal-Wallis tests were conducted for both the original summary measures data (Tables 5a to 5d – Appendix A) and the regenerated summary measures data (Tables 7a to 7d – Appendix A) for each respective outcome variable. This was done using the same SAS code as in section 4.3. The results from the normal tests and the Kruskal-Wallis tests on the data, both before and after data replacement, are also displayed in Tables 5.1.1-5.1.4 below for HR, SBP, DBP and dietary response respectively. Any significant results are highlighted for all tests.

Of the various univariate approaches applied to the data, tests on each of the summary measures was considered to be the only univariate testing of any use. In the case of univariate testing of time, any missing data lead to imbalance and inconsistency between groups. Univariate testing at each time point was not of any interest while testing for group differences. Missing data and imbalance were not an

issue with the univariate summary measures analysis that was applied to the data. This was because the dimension of the summary statistic vector was small compared to the sample size of treatment groups, hence, one could arrive at reasonable conclusions via asymptotic tests. While applying these there is no loss of generality in assuming the summary statistic vector to be normal even when this is not so. A non-parametric Kruskal-Wallis approximation of the Chi-squared test in a 1-way ANOVA approach was taken to analyse the data by testing between treatment groups. The tests conducted were similar to those conducted at each univariate time point in Tables 1a-1d and 2a-2d (Appendix A) and also in Tables 4.2.1-4.2.4 [section 4.3], using Proc NPAR1WAY with the WILCOXON option. This method was adequate to test for treatment differences in a non-balanced situation and the condition of normality, as implied earlier, was not of great importance. The assumption of normality did not need to be met in order to use this method.

It was then decided to summarise the summary measures by centre and treatment for data set A. Since there were no differences in the results from the original data and the data after imputing missing records, this by centre summary was displayed in Table 6a to 6c (Appendix A) for the original HR, SBP and DBP data only. Tables 5.1.1-5.1.3 below also show the respective results of all Kruskal-Wallis tests per centre for summary measures on the original HR, SBP and DBP data.

Block charts were produced overall and by treatment / therapy group for both the original and imputed data sets for each summary measure. It could be seen that there were no vast differences before and after imputation so only the charts of the original data (data sets A and B) are displayed for this thesis. Block charts were produced for the overall original HR, SBP, DBP and dietary response data and are displayed in Figures 5.1.1-5.1.4 below. Here, Figures C and D show the mean and median respectively, Figures E and F show the minimum and maximum and Figures G and H show the lower quartile and upper quartile. The block charts for baseline data from the original data set only are displayed in Figure A and those displayed in Figure B represent the mean change from baseline. Similar block charts by treatment groups were produced for the original HR, SBP, DBP and dietary response data and are displayed in Figures 5.2.1-5.2.4 below.

5.1.1: Heart Rate (beats/minute)

The normal tests in Table 4.2.1 [section 4.3.1] above showed that the baseline data for each treatment group was normally distributed (p>0.260). From conducting the Kruskal-Wallis test on the data it could be seen that there were no significant treatment differences for heart rate at baseline (p>0.918).

Table 5.1.1
Normal Tests Per Treatment and Kruskal-Wallis Tests For Each Summary Measures P-Values to Compare Before and After Data Generation: Heart Rates (b/m)

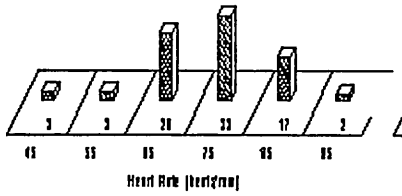
Summary Measure	Dataset	Treatment				K-Wallis
		1	2	3	4	
Change	Before	**0.002***	**0.011***	0.475	**0.013***	0.161
	Centre 1					0.467
	Centre 2					0.103
	After	**0.006***	**0.011***	0.506	**0.010***	0.173
Mean	Before	0.528	0.486	0.204	0.680	0.985
	Centre 1					0.883
	Centre 2					0.630
	After	0.583	0.488	0.142	0.639	0.978
Median	Before	0.809	0.421	0.222	0.504	0.927
	Centre 1					0.832
	Centre 2					0.497
	After	0.766	0.390	0.178	0.504	0.931
Minimum	Before	0.799	0.789	0.963	0.801	0.608
	Centre 1					0.767
	Centre 2					0.360
	After	0.799	0.789	0.797	0.801	0.586
Maximum	Before	0.656	**0.006***	0.186	0.400	0.739
	Centre 1					0.884
	Centre 2					0.836
	After	0.656	**0.006***	0.131	0.400	0.743
Lower Quartile	Before	0.661	0.912	0.353	0.429	0.904
	Centre 1					0.706
	Centre 2					0.843
	After	0.573	0.861	0.199	0.429	0.886
Upper Quartile	Before	0.721	0.428	0.268	0.753	0.987
	Centre 1					0.759
	Centre 2					0.481
	After	0.736	0.469	0.235	0.729	0.984

Statistical summaries and tests before and after replacement can be seen in Tables 5a and 7a respectively (Appendix A). Summary measures on the data, both before and after replacement, were tested using normal and Kruskal-Wallis tests (Tables 5.1.1). Normal tests and K-Wallis tests gave similar results both before and after replacement for heart rate data. This was also seen with the figures, hence only figures on the original data are displayed. There were no treatment differences for any of the summary measures mentioned above.

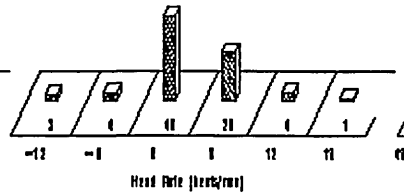
Figure 5.1.1

Block Charts of Overall Heart Rate (beats/min) Values : Original Data

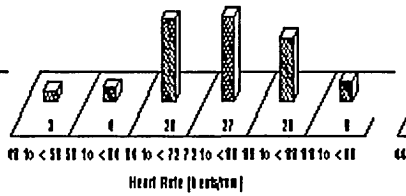
A : Baseline



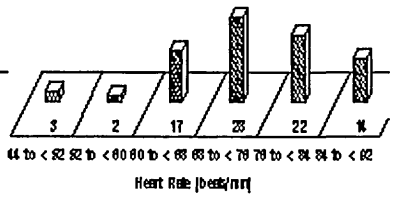
B : Change



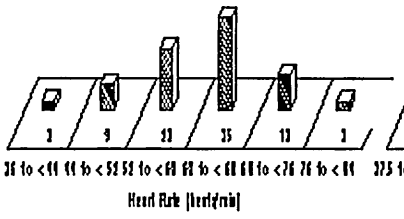
C : Mean



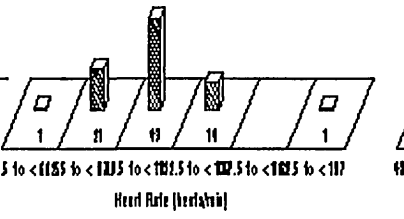
D : Median



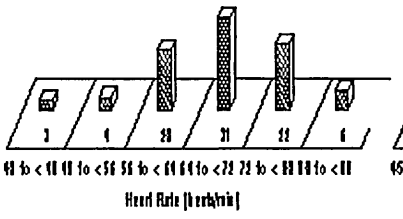
E : Minimum



F : Maximum



G : Lower Quartile



H : Upper Quartile

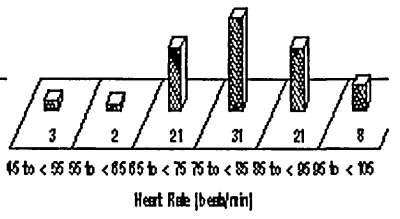
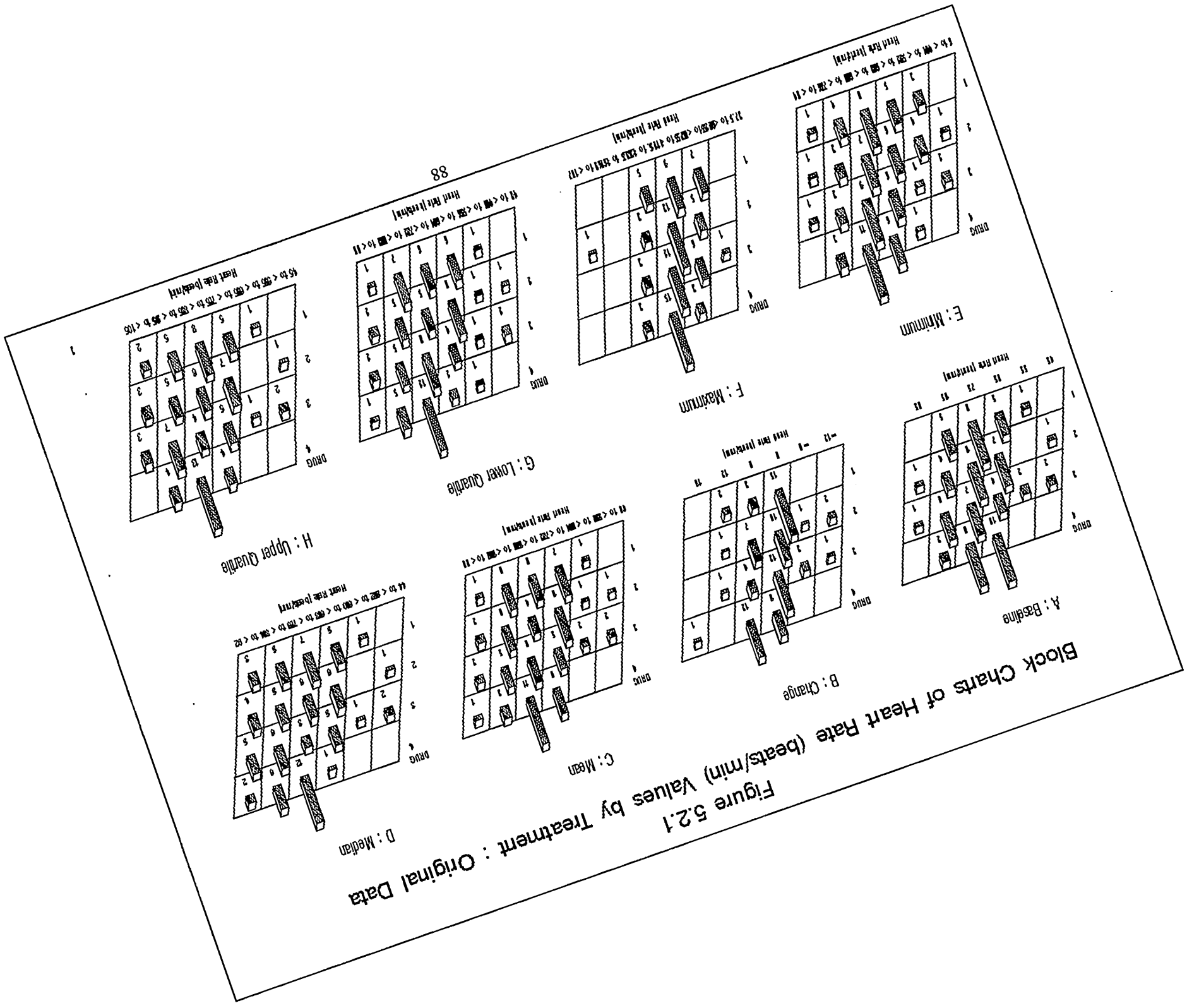


Figure 5.2.1
Block Charts of Heart Rate (beats/min) Values by Treatment : Original Data



Summary measures were obtained for the on-treatment data across time. These summary measures were displayed in the box-plots above (Figures 5.1.1B to 5.1.1H and 5.2.1B to 5.2.1H). Note that the axes on the block charts are not consistent for each summary measure.

From the normal and Kruskal-Wallis tests displayed in Table 5.1.1 above it can be seen there were no treatment differences in the mean, median, lower quartile, upper quartile or minimum heart rate (b/m) responses. The data was also normally distributed per treatment for all these summary measures.

For the maximum readings (Figures 5.1.1F and 5.2.1F), there was one outlier on drug 2 that ranged from 162.5 to 187.5 beats/min and another individual on drug 3 had a reading between 37.5 and 62.5 beats/min. All other readings ranged from 62.5 to 137.5 beats/min. The normal tests in Table 5.1.1 also show that the maximum response on drug 2 was not normally distributed. There were no treatment differences in the maximum heart rate readings.

Figures 5.1.1B and 5.2.1B describe the summary statistic change in mean from baseline. From Figure 5.2.1B, it can be seen that 1 individual on drug 4 had an outlier value for change of mean value which ranged between 14 to 18. All other changes ranged from –14 to 14. Table 5.1.1 showed that all treatments apart from drug 3 had a skewed distribution for the change in mean from baseline. This can also be seen in Figure 5.2.1B. There were no treatment differences in the mean change from baseline for heart rate data (Table 5.1.1).

The summary measures on the data before replacing missing data were observed for the original data by centre (Table 6a-Appendix A). There are some inconsistencies with the normality tests per centre (see Table 6a-Appendix A) compared to the results on the original data. This is not however of great concern here. Tests for treatment differences by centre are also displayed in Table 5.1.1 above. It can be seen that the summary measures did not have any significant treatment differences for either centre 1 or 2. This agrees with the results on the overall data.

In conclusion, there was only evidence of a non-normal distribution for the maximum data for drug 2 and the change in mean from baseline for all treatments apart from drug 3. It can be seen that all summary measures, on both the overall data and data by centre, showed no significant evidence of treatment differences as with the tests at individual time points in the previous chapter. All results on the summary measures were consistent both before and after data replacement. This agrees with the findings on the univariate time points of data.

5.1.2: Systolic Blood Pressure (mmHg)

The normal tests in Table 4.2.2 [section 4.3.2] above showed that the data at baseline for only drug 3 were not normal (p=0.041) and were normally distributed for all other drugs (p>0.066). This can also be seen in Figure 5.2.2A. It could be seen, from the Kruskal-Wallis test, that there were no significant treatment differences for systolic BP at baseline (p>0.857).

Table 5.1.2
Normal Tests Per Treatment and Kruskal-Wallis Tests For Each Summary Measures P-Values to Compare Before and After Data Generation: Systolic BP (mmHg)

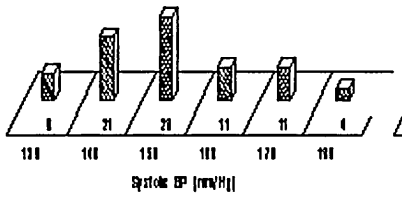
Summary Measure	Dataset	Treatment				K-Wallis
		1	2	3	4	
Change	Before	0.163	**0.003***	0.376	0.259	**<0.001***
	Centre 1					**0.002***
	Centre 2					0.061
	After	0.253	**0.003***	0.534	0.273	**<0.001***
Mean	Before	0.967	0.996	0.531	0.171	**0.015***
	Centre 1					**0.025***
	Centre 2					0.576
	After	0.983	0.996	0.633	0.146	**0.016***
Median	Before	0.770	0.975	0.329	0.358	**0.015***
	Centre 1					**0.016***
	Centre 2					0.455
	After	0.824	0.976	0.324	0.349	**0.012***
Minimum	Before	0.094	0.766	0.166	0.900	**0.022***
	Centre 1					0.188
	Centre 2					0.135
	After	0.094	0.766	0.229	0.900	**0.023***
Maximum	Before	0.473	0.936	0.727	0.788	0.065
	Centre 1					**0.042***
	Centre 2					0.621
	After	0.473	0.936	0.703	0.788	0.063
Lower Quartile	Before	0.969	0.998	0.697	0.089	**0.012***
	Centre 1					**0.029***
	Centre 2					0.380
	After	0.981	0.997	0.889	0.099	**0.013***
Upper Quartile	Before	0.812	0.907	0.458	0.369	**0.030***
	Centre 1					**0.017***
	Centre 2					0.691
	After	0.870	0.913	0.394	0.347	**0.030***

Statistical summaries and tests before and after replacement can be seen in Tables 5b and 7b respectively (Appendix A). Summary measures on the data, both before and after replacement, were tested using normal and Kruskal-Wallis tests (Tables 5.1.2). Normal tests and K-Wallis tests gave similar results for systolic BP data both before and after replacement. This was also seen with the figures, hence only figures on the original data are displayed.

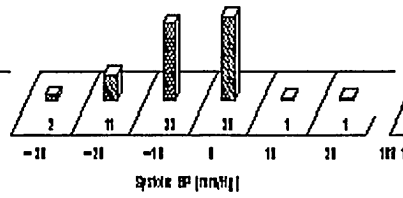
There were significant treatment differences for all systolic BP summary measures described apart from the baseline reading and the maximum response (Tables 4.2.2 and 5.1.2).

Figure 5.1.2
Block Charts of Overall Systolic BP (mm/Hg) Values : Original Data

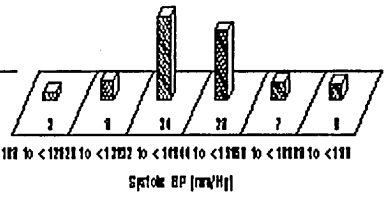
A : Baseline



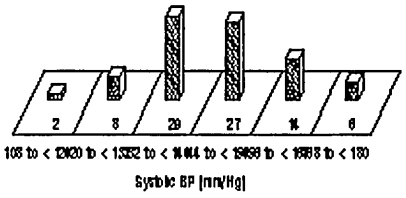
B : Change



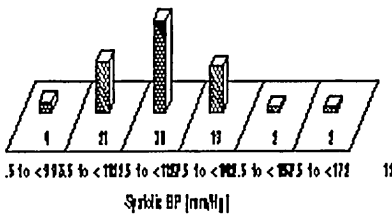
C : Mean



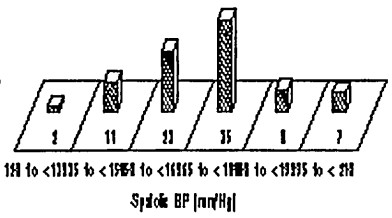
D : Median



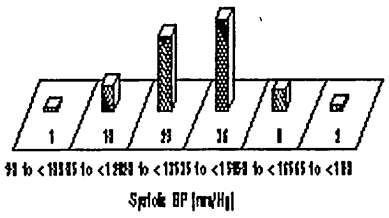
E : Minimum



F : Maximum



G : Lower Quartile



H : Upper Quartile

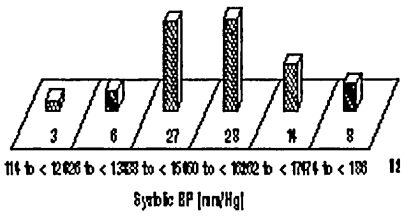
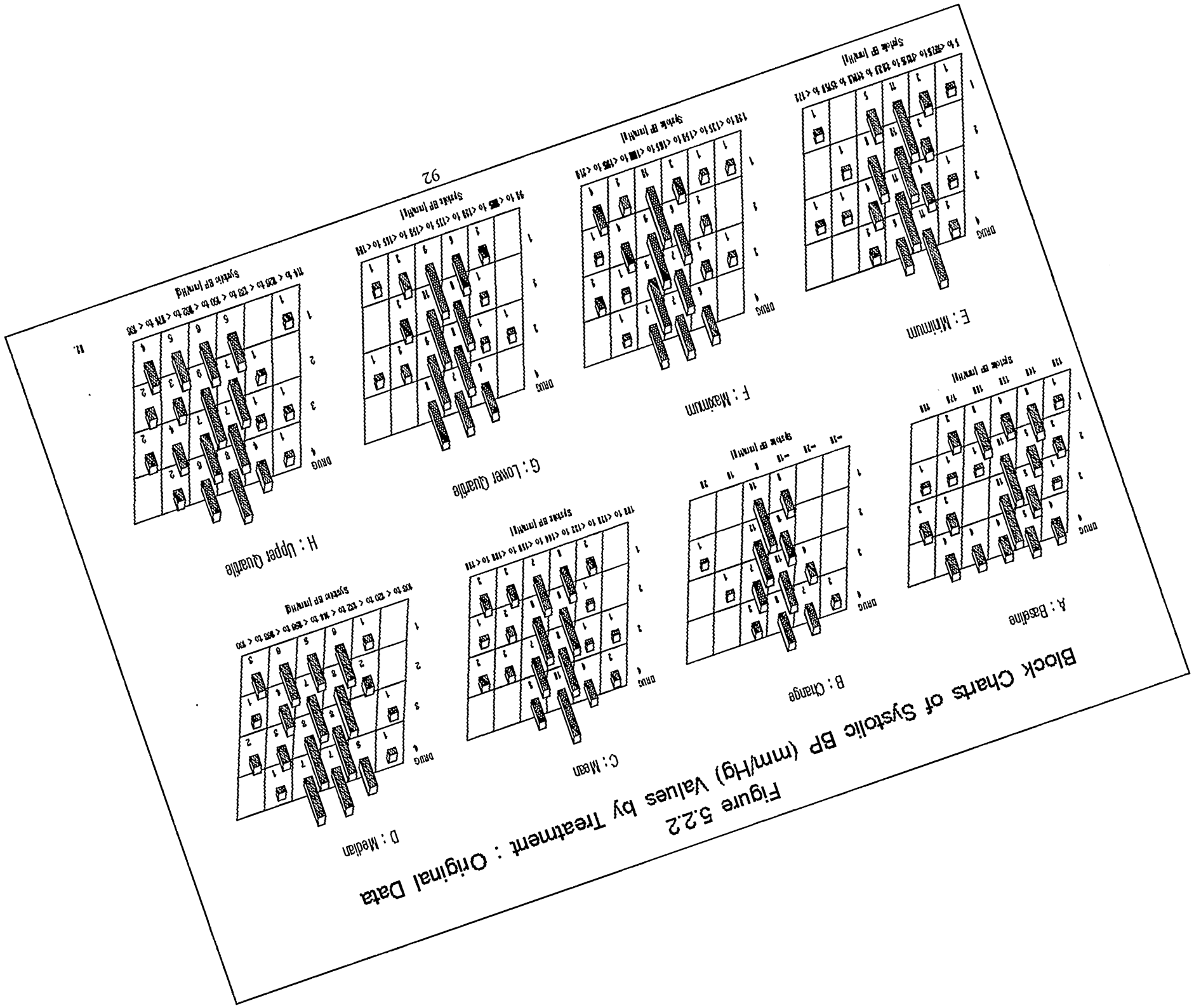


Figure 5.2.2
Block Charts of Systolic BP (mm/Hg) Values by Treatment : Original Data



The mean (Figure 5.1.2C), median (Figure 5.1.2D), minimum (Figure 5.1.2E), maximum (Figure 5.1.2F), lower quartile (Figure 5.1.2G) and upper quartile (Figure 5.1.2H) response block charts for overall data appear to be normally distributed. The normal tests shown in Table 5.1.2 above all agree with this statement ($p>0.089$) for all treatments both before and after imputing missing data.

There was only evidence of a non-normal distribution for the change in mean from baseline for drug 2 and this was consistent for the data before and after replacing missing records ($p=0.003$). This can be seen clearly in Figure 5.2.2B where drug 2 has one outlying value of mean change from baseline. The outlier reading was between 15 and 25 mmHg, whereas all other observations for drug 2 ranged from -15 to 5 mmHg. Figure 5.1.2B, shows that the overall mean change data was slightly skewed. From observing Figure 5.2.2B it can be seen that drug 4 had the largest change from baseline.

It can be seen that all summary measures in Table 5.1.2 above, apart from the maximum response showed significant treatment differences both before and after data replacement. For the mean ($p=0.015$ before and $p=0.016$ after), for the median ($p=0.015$ before and 0.012 after), for the minimum ($p=0.022$ before, $p=0.023$ after) and for the lower quartile ($p=0.012$ before and $p=0.013$ after). For the upper quartile ($p=0.030$ both before and after) and for the change in mean from baseline ($p<0.001$ both before and after).

The summary measures on the data before replacing missing data were observed by centre for the original data Table 6b (Appendix A). The Kruskal-Wallis test results on the data by centre are also displayed in Table 5.1.2 above. The summary measures did not show significant treatment differences for all data in centre 2 and all the data apart from minimum response in centre 1 had a significant treatment difference.

5.1.3: Diastolic Blood Pressure (mmHg):

From the block charts below of the overall (Figure 5.1.3A) and by treatment (Figure 5.2.3A) readings at baseline, it appears as if the data was normally distributed. The normal tests conducted in Table 4.2.3 [section 4.3.3] above confirmed this statement ($p>0.128$ before and after imputing missing data). There were also no significant treatment differences at baseline ($p=0.900$ before and $p=0.894$ after imputing missing data) using the Kruskal-Wallis test for significance in Table 4.2.3.

Table 5.1.3
Normal Tests Per Treatment and Kruskal-Wallis Tests For Each Summary Measures P-Values to Compare Before and After Data Generation: Diastolic BP (mmHg)

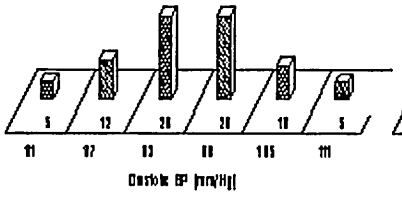
Summary Measure	Dataset	Treatment				K-Wallis
		1	2	3	4	
Change	Before	0.801	**0.001***	**0.036***	0.196	**<0.001***
	Centre 1					**<0.001***
	Centre 2					**0.034***
	After	0.739	**0.002***	**0.026***	0.174	**<0.001***
Mean	Before	0.102	0.608	0.552	0.293	**0.015***
	Centre 1					**0.044***
	Centre 2					0.589
	After	0.135	0.645	0.722	0.299	**0.015***
Median	Before	0.509	0.802	0.491	0.755	**0.029***
	Centre 1					**0.041***
	Centre 2					0.735
	After	0.545	0.790	0.591	0.767	**0.022***
Minimum	Before	0.626	0.701	0.969	0.516	**0.006***
	Centre 1					0.189
	Centre 2					0.059
	After	0.626	0.701	0.934	0.516	**0.008***
Maximum	Before	**0.019***	0.462	0.077	0.608	**0.002***
	Centre 1					**0.008***
	Centre 2					0.341
	After	**0.019***	0.462	0.055	0.608	**0.002***
Lower Quartile	Before	0.412	0.806	0.411	0.233	0.086
	Centre 1					0.427
	Centre 2					0.357
	After	0.402	0.794	0.560	0.270	0.071
Upper Quartile	Before	0.050	0.699	0.959	0.856	**0.026***
	Centre 1					**0.017***
	Centre 2					0.805
	After	0.054	0.715	0.976	0.889	**0.022***

Statistical summaries and tests before and after replacement can be seen in Tables 5c and 7c respectively (Appendix A). Summary measures on the data, both before and after replacement, were tested using normal and Kruskal-Wallis tests (see Tables 5.1.3 above). Normal tests and K-Wallis tests gave similar results both before and after replacement for diastolic BP data. This was also seen with the figures, hence only figures on the original data are displayed.

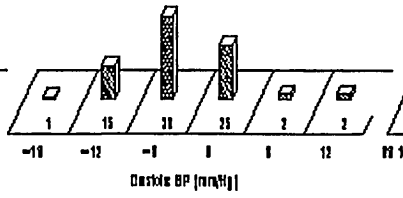
There were significant treatment differences for all diastolic BP summary measures described apart from the baseline and lower quartile readings (Tables 4.2.3 and 5.1.3).

Figure 5.1.3
Block Charts of Overall Diastolic BP (mm/Hg) Values : Original Data

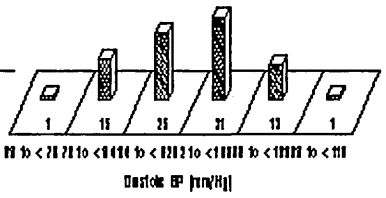
A : Baseline



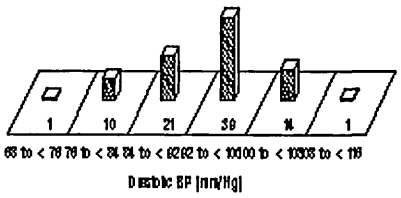
B : Change



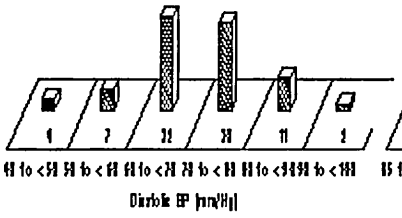
C : Mean



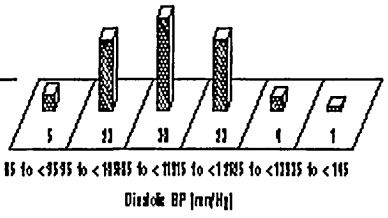
D : Median



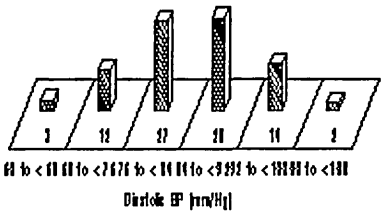
E : Minimum



F : Maximum



G : Lower Quartile



H : Upper Quartile

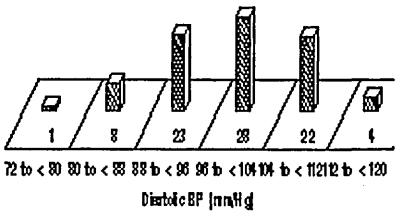
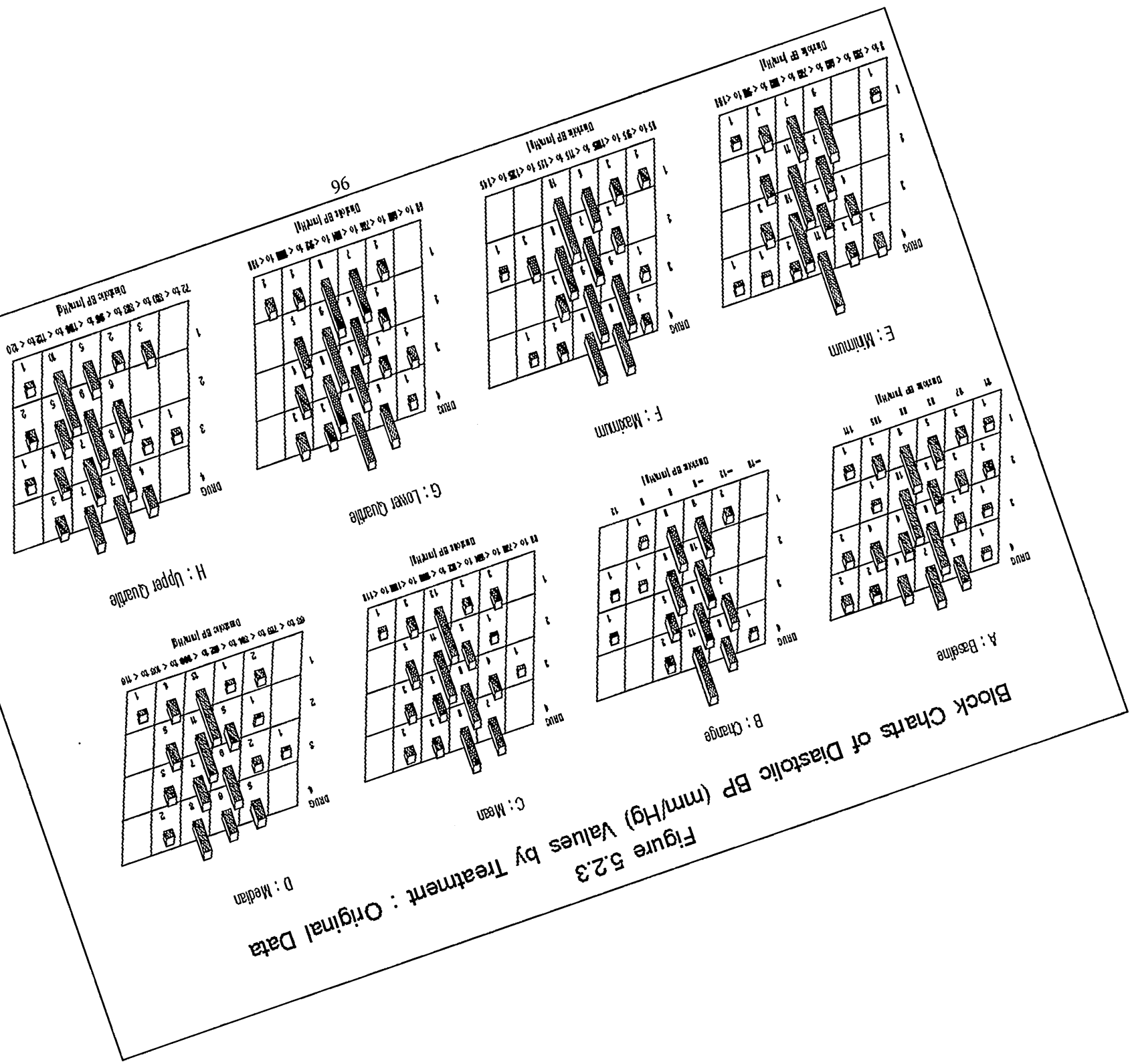


Figure 5.2.3
Block Charts of Diastolic BP (mm/Hg) Values by Treatment : Original Data



For the lower quartile for diastolic BP in Table 5.1.3 above it can be seen that the data is normally distributed for all four drugs both before ($p>0.233$) and after ($p>0.270$) imputing missing records. The Kruskal-Wallis tests show no significant treatment differences both before ($p=0.086$) and after imputing missing data ($p=0.071$). Figures 5.1.3G and 5.2.3G agree with this statement.

For the original data, the change in mean from baseline (Figure 5.2.3B) is slightly skewed for drugs 2 ($p=0.01$) and 3 ($p=0.036$) and the maximum (Figure 5.2.3F) data is skewed for drugs 1 ($p=0.019$). The results after imputing missing data also give similar conclusions. All other summary measures (mean, median, minimum and upper quartile) appeared to be normally distributed overall and by treatment group. The mean, median, minimum, maximum, change in mean from baseline and upper quartile responses on both the original data ($p<0.029$) and the data after imputing missing records ($p< 0.022$) all showed significant treatment differences.

The summary measures on the data before replacing missing data were observed by centre for the original data (Table 6c-Appendix A). The Kruskal-Wallis tests of treatment differences per centre are also displayed in Table 5.1.3 above. There was not enough evidence to suggest a treatment difference for both the lower quartile ($p=0.427$) and minimum ($p=0.189$) response data for individuals in centre 1. The only summary measure for which there was a significant treatment difference in centre 2 was the change in mean from baseline ($p=0.034$). The inconsistency in findings between centres is nothing to be concerned about.

In conclusion, there were significant treatment differences in the mean, mean change from baseline, median, minimum, maximum and upper quartile for diastolic BP.

5.1.4: Dietary Response

A block-chart of the baseline reading is displayed in Figures 5.1.4A and 5.2.4A. Table 4.2.4 [section 4.3.4] shows the results of the normal test that was conducted on the baseline data ($p>0.664$). This indicates that all data are normally distributed. The Kruskal-Wallis test that was conducted on the data showed that there was not significant evidence to suggest a treatment difference at baseline ($p=0.539$). Statistical summaries and tests before and after replacement can be seen in Tables 5d and 7d respectively (Appendix A). Summary measures on the data, both before and after replacement, were tested using normal and Kruskal-Wallis tests (see Tables 5.1.4 below). Normal tests and K-Wallis tests gave similar results both before and after replacement for dietary response data. This was also seen with the figures, hence only figures on the original data are displayed below.

Table 5.1.4
Normal Tests Per Treatment and Kruskal-Wallis Tests For Each Summary Measures P-Values to Compare Before and After Data Generation: Dietary Response

Summary Measure	Dataset	Therapy			K-Wallis
		1	2	3	
Change	Before	0.527	0.589	0.679	<0.001*
	After	0.491	0.775	0.855	<0.001*
Mean	Before	0.386	0.250	0.498	<0.001*
	After	0.444	0.252	0.795	<0.001*
Median	Before	0.235	0.241	0.934	<0.001*
	After	0.474	0.116	0.996	<0.001*
Minimum	Before	0.638	0.217	0.574	<0.001*
	After	0.638	0.358	0.546	<0.001*
Maximum	Before	0.060	0.402	0.335	<0.001*
	After	0.060	0.457	0.562	<0.001*
Lower Quartile	Before	0.937	0.665	0.676	<0.001*
	After	0.932	0.506	0.884	<0.001*
Upper Quartile	Before	0.526	0.307	0.726	<0.001*
	After	0.526	0.279	0.717	<0.001*

All results were normal both before and after imputing missing records. There were significant treatment differences noted for all summary measures. Both the results before and after imputing missing records gave similar findings.

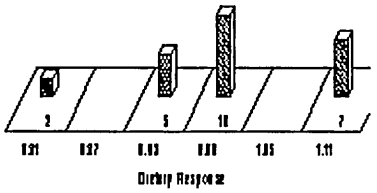
All normal tests that were conducted on the summary measures on the data (Table 5.1.4 above) showed that there was not enough evidence to suggest that the data was skewed. It can be seen from all block charts that were produced by therapy groups (Figures 5.2.4B-5.2.4H) that there was a treatment difference and this was confirmed by the Kruskal-Wallis tests ($p<0.001$ in all cases). In all cases, group 3 had "lower" results than group 2, which had "lower" results than group 1.

These findings agree with the findings at each univariate time point, apart from times 0 and 1, for dietary response data as displayed in Table 4.2.4 [section 4.3.4 above]. Figure 5.2.4A below shows the distribution of dietary response by treatment at baseline or time 0. There appear to be no treatment differences, confirming the findings in Table 4.2.4.

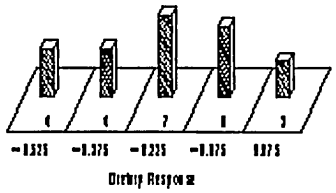
The univariate summary measures on the data were tested both before and after data replacement and the results were again consistent. There was a significant treatment difference for each summary measure (mean, median, minimum, maximum, lower quartile, upper quartile and change in mean from baseline) that was tested both before and after data replacement (Table 5.1.4). Only the baseline measurement showed no significant treatment difference (Table 4.2.4).

Figure 5.1.4
Block Charts of Overall Dietary Response Values : Original Data

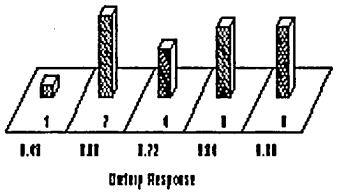
A : Baseline



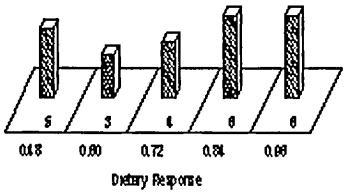
B : Change



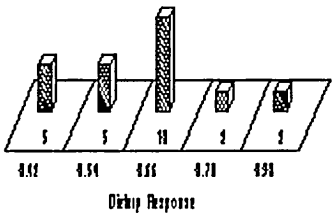
C : Mean



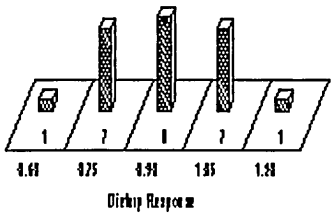
D : Median



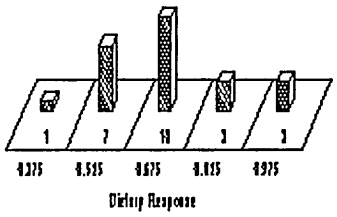
E : Minimum



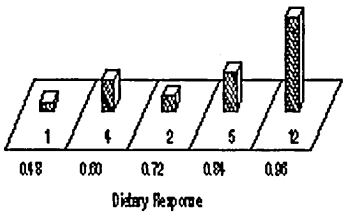
F : Maximum

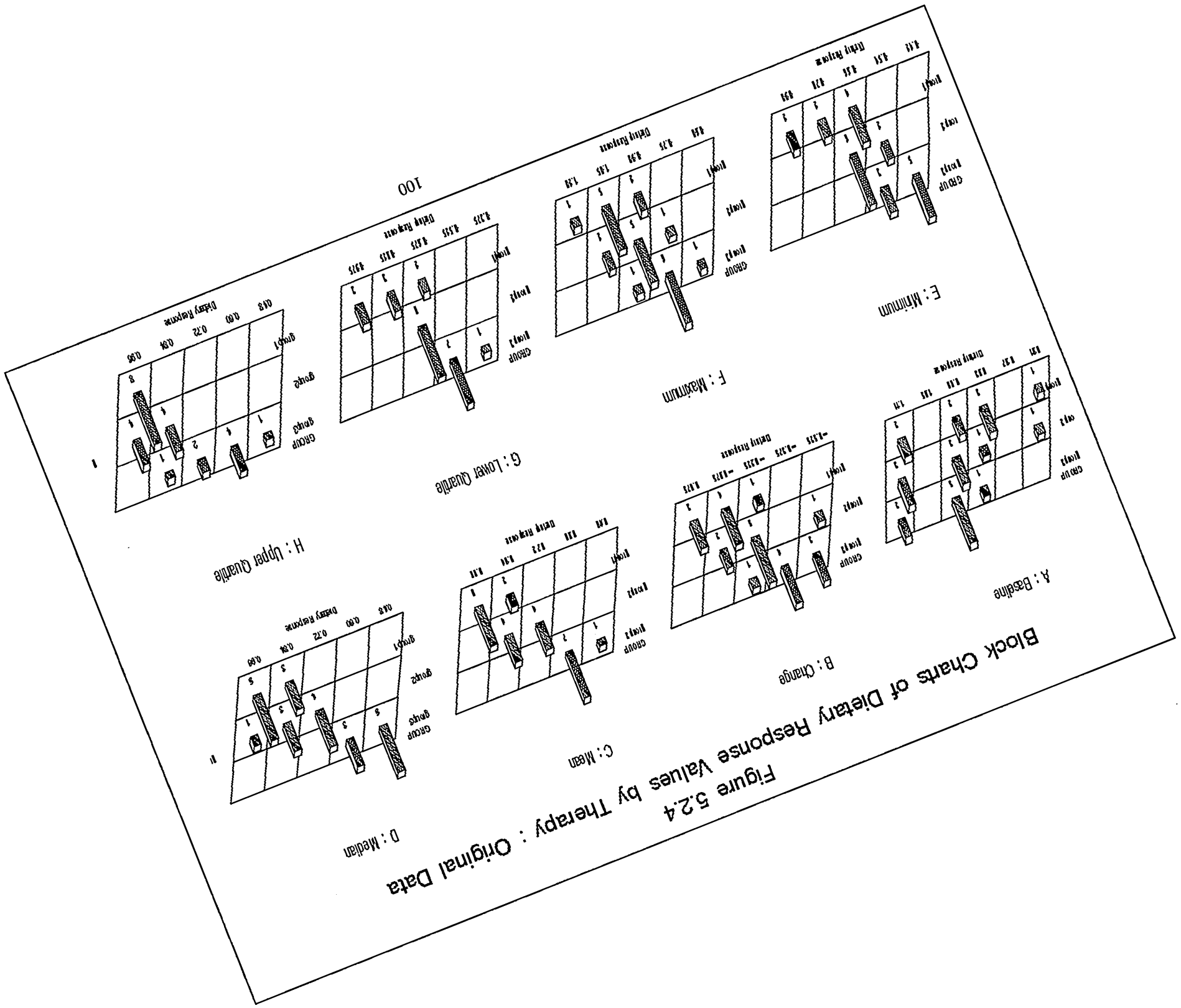


G : Lower Quartile



H : Upper Quartile




Block Charts of Dietary Response Values by Therapy : Original Data
A : Baseline
B : Change
C : Mean
D : Median
E : Minimum
F : Maximum
G : Lower Quartile
H : Upper Quartile
100

5.2 Categorical Data Analysis

As previously mentioned, all categorical analyses were conducted on only the variables in data set A and all categorical data are obtained from the original data before imputing missing records.

From Listing 3.3 [section 3.2] it can be seen that the data at each time point was categorised as 'low', 'normal' or 'high'. A block chart of the frequency of individuals with vital signs of each level at the baseline reading are displayed in Figures 5.3.1A, 5.3.2A and 5.3.3A for overall data and Figures 5.3.1B, 5.3.2B and 5.3.3B by treatment for heart rate, systolic and diastolic BP respectively.

Following the categorisation above, data set A was set up in the format as described in Listing 3.5 [section 3.3.2]. There were three summary measures that were looked into. These were 'NH','NL' and 'NN', which were the number of abnormally 'HIGH', 'LOW' and 'NORMAL' readings over the study per individual. Each value per individual could range anything from 0 to 24 but the sum of all three readings had to be less than or equal to 24.

The frequencies of occurrence of an event of 'low', 'normal' or 'high' readings respectively were treated as continuous data and analysed as such. Tables 13a to 13c (Appendix A) show findings for the Kruskal-Wallis tests to test for treatment differences overall and by centre for the frequency of occurrence of each of these events for heart rate, SBP and DBP respectively.

The frequencies of 'low', 'normal' and 'high' results per individual by treatment group per centre are displayed in Figures 5.4.1 to 5.4.3 below.

It was decided that all further statistical tests were to only be conducted using 'NH' and 'HIGH'.

An approach similar to the response features analysis was applied to the data. Hence, the main measure considered being of importance for analysis was:

a) Number of Overall Abnormally High Readings On-Treatment.

The summary statistic for the frequency of abnormally 'high' on-treatment results per individual, where each response value 'NH' could range from 0 to 24, was calculated as described above. Scatterplots of this variable by centre are shown in Figures 5.4.1A1 to 5.4.3A2 below. Tables 14a to 14c (Appendix A) show the distribution of the number of abnormally 'high' readings per treatment group and overall for heart rate, systolic and diastolic BP respectively. The frequency of occurrence of abnormally 'high' results per individual 'NH' was treated as a continuous variable. Tables 15a-15c (Appendix A) show the contingency tables of the categorised frequency of the number of abnormally 'high' readings. A Chi-

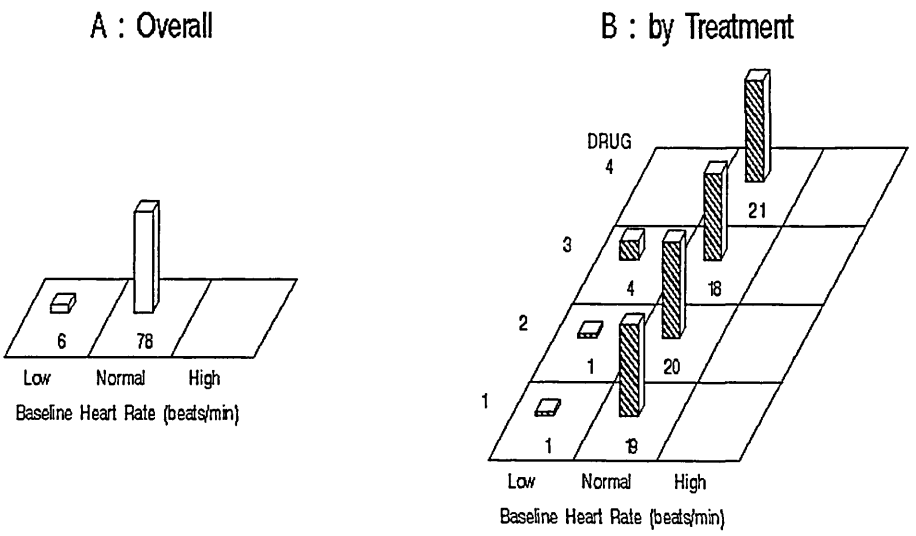
squared test was conducted to test for the relationship between treatment groups. The tests were conducted overall and by centre and the p-values are also displayed in these tables.

b) Greater than 50% or greater than 75% of Abnormally High Results over the study.

The number of abnormally 'high' results were divided by the number of available results and multiplied by 100. The result gave a percentage. If the result was greater than 50% then the variable 'HALFABN' was "yes" and otherwise was set to "no". The same approach was taken to calculate the variable 'QRTABN' when the result was greater than 75%. Chi-squared tests were conducted on the frequency of individuals that fit each criteria mentioned. This was only applied for systolic and diastolic BP since there were few occurrences (less than 50% in all cases) of abnormally high heart rates. See Tables 16b and 16c (Appendix A) for these respective frequency tables for systolic and diastolic BP.

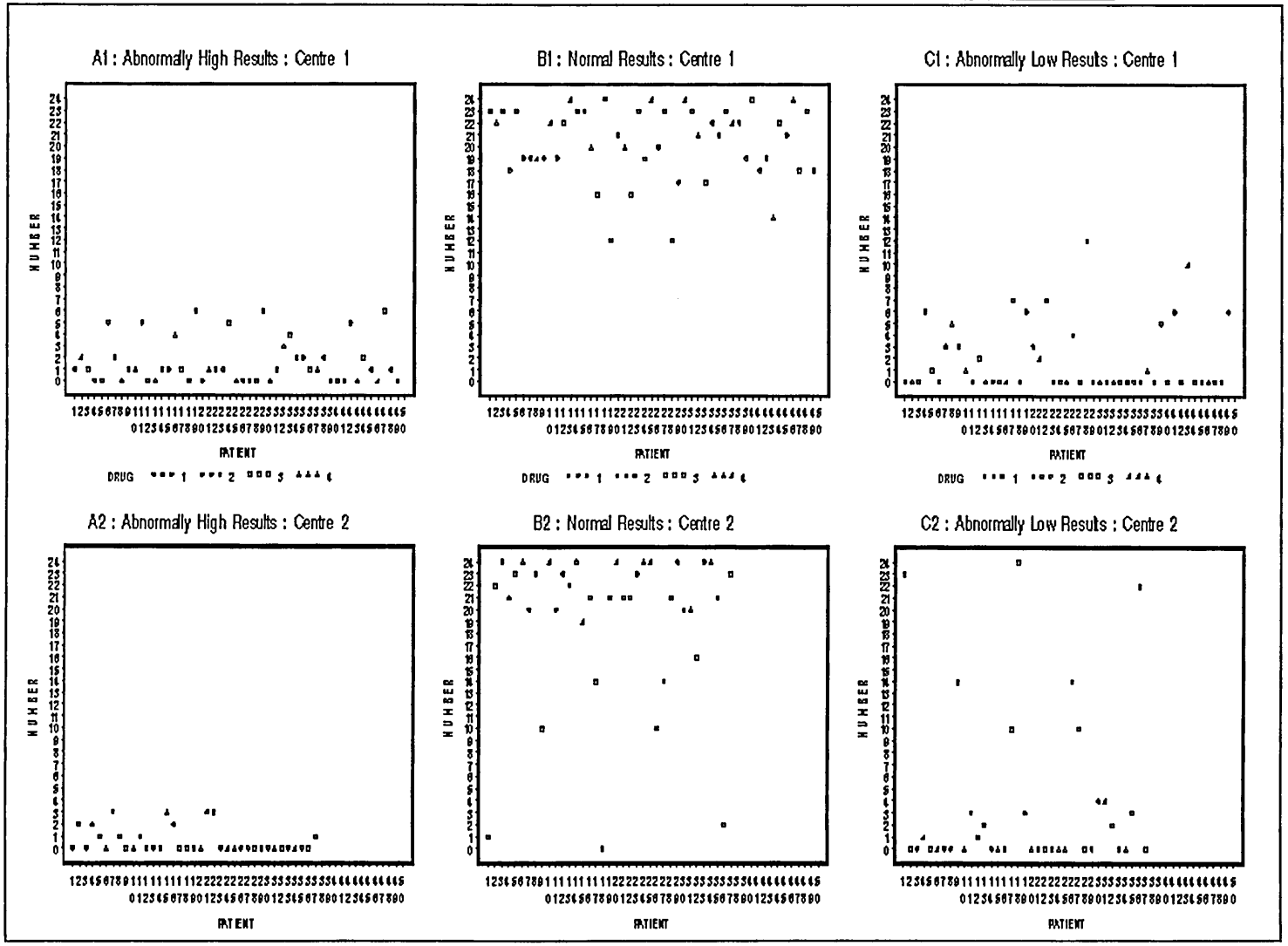
5.2.1: Heart Rate (beats/minute)

Figure 5.3.1
Block Charts of Level of Readings for Baseline Heart Rate (beats/min)
Original Data



The data was categorised as being 'low', 'normal' or 'high' at each visit. From the Figure 5.3.1 above, it can be seen that there were no individuals with abnormally 'high' results at baseline for heart rate (b/m). Most individuals (78 out of 84) had 'normal' heart rate measurements at baseline. Only 6 of the 84 individuals with a baseline measurement had a 'low' result and 4 of these were on drug 3. None of the individuals on drug 4 had a 'low' reading at baseline.

Figure 5.4.1: Scatter-Plot of Levels of Abnormality Per Patient Per Centre (n=86) : Heart Rate (b/m)



On observing the scatter-plots above (Figure 5.4.1), it can be seen that the majority of individuals on-treatment results were 'normal' for heart rate (Figures 5.4.1B1 and 5.4.1B2).

It was assumed that the frequencies of 'normal', 'high' or 'low' on-treatment results per individual were continuous data. Following the Kruskal-Wallis tests on this data (from Table 13a - Appendix A) there was significant evidence to suggest a treatment difference overall (p=0.017) for the number of 'normal' on-treatment results. This was also the case for centre 2 (p=0.031) (see Figure 5.4.1B2). In both cases drugs 2 and 3 tended to result in a lower number of 'normal' results and drugs 1 and 4 seemed to give more 'normal' readings per individual.

All other tests in Table 13a (Appendix A) showed no significant treatment differences for the total number of 'low' or 'high' results for any centre or overall (p>0.316).

From the 49 individuals in centre 1, only 4 individuals on drug 4 and 3 individuals on drug 2 had at least one 'low' result (Figure 5.4.1C1). The maximum number of 'low' results for any individual in centre 1 was 4. Slightly more (16 out of 37) individuals in centre 2 had at least one 'low' blood pressure measurement (Figure 5.4.1C2). There were 4 individual on drug 3, 2 individuals on drug 2 and 1 individual on drug 1 with more than 9 'low' readings. Nine individuals had between 1 and 4 'low' readings and the remaining 21 out of a total of 37 individuals had no 'low' readings at all. From Figure 5.4.1C2 it can be seen that for patients on drugs 1 and 3 in centre 2 there tended to be greater occurrence of abnormally 'low' results while on-treatment. However, 'low' results are not of much concern.

Only the 'high' results were considered worthwhile to report since these mean there is a problem or abnormality in the data. From the results in Table 13a (Appendix A), the maximum number of 'high' heart rate results for an individual was 6 out of a possible 24 on-treatment time measurements. This can be seen clearly in Figure 5.4.1A1 and A2 below. Out of 37 individuals in centre 2 (Figure 5.4.1A2) there were 11 with at least one 'high' reading compared to 31 out of 49 individuals in centre 1 (Figure 5.4.1A1) with at least one 'high' reading. More individuals in centre 1 had at least one abnormally 'high' reading. The maximum number of 'high' results for any individuals in centre 1 was 6. The maximum number of 'high' responses for individuals in centre 2 was 3.

A frequency table of the total number of abnormally 'high' results is shown in Table 14a (Appendix A). Of the 86 individuals in the study, 44 had no abnormally 'high' readings. From Table 15a (Appendix A), it can be seen that there was no relationship between frequency of occurrence per treatment group either overall or by centre (p>0.421).

It could be seen that none of the patients were classified as having greater than 50% or 75% abnormally 'high' heart rate readings, hence, no further analyses were conducted on these outcomes.

5.2.2: Systolic Blood Pressure (mmHg)

Figure 5.3.2
Block Charts of Level of Readings for Baseline Systolic Blood Pressure(mmHg)
Original Data

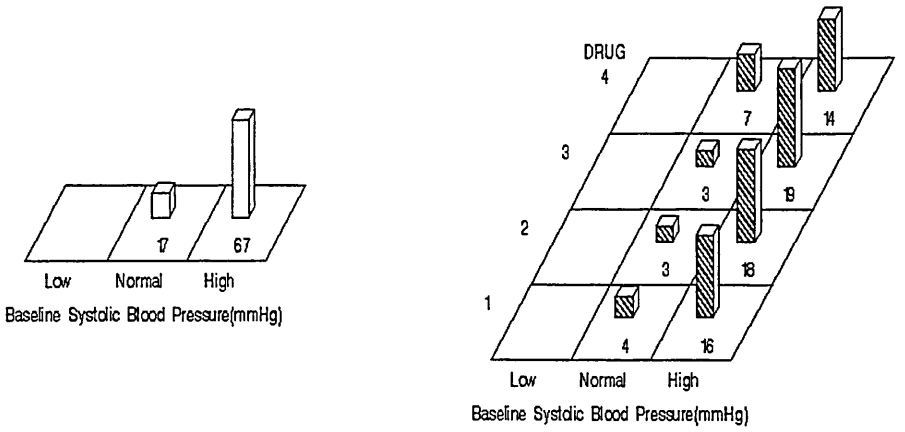
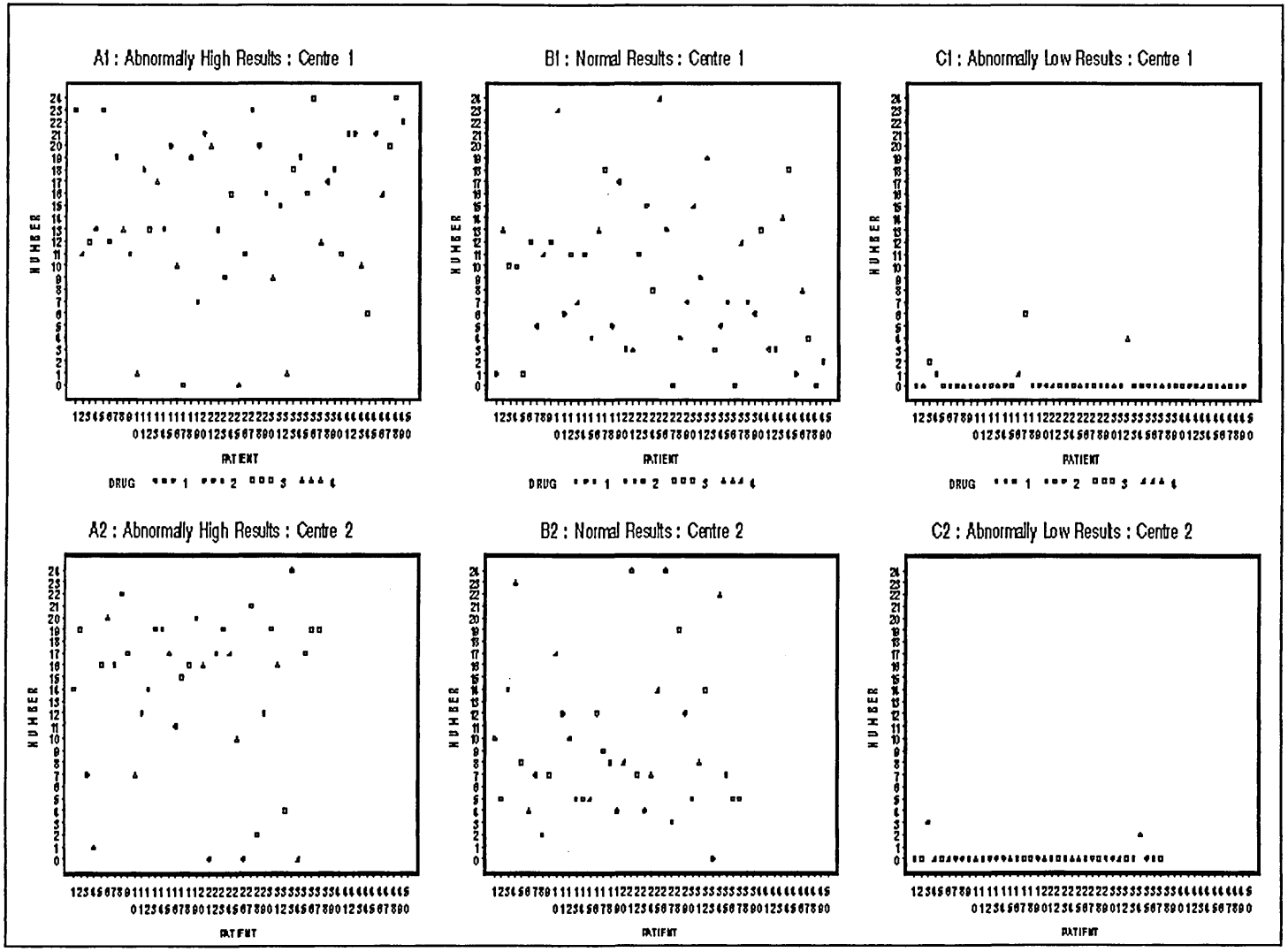


Figure 5.3.2 above shows that there were no 'low' systolic BP readings at baseline. Only 17 of the 84 individuals with a baseline measurement had a 'normal' baseline result and the remaining 67 had a 'high' baseline response. There appeared to be an equal distribution of results across treatment groups.
The total numbers of on-treatment responses per individual were calculated for 'low' (Figures 5.4.2C1 and 5.4.2C2), 'normal' (Figures 5.4.2B1 and 5.4.2B2) and 'high' (Figures 5.4.2A1 and 5.4.2A2) responses by centre. From looking at the scatter-plots in Figure 5.4.2 below, it can be seen that most of the results for individuals systolic blood pressure measurements were either 'normal' or 'high'. Only 5 out of 49 individuals in centre 1 and 2 of the 37 individuals in centre 2 had at least one 'low' reading. The maximum number of 'low' readings for any individual was 6 for centre 1 and 3 for centre 2.

Figure 5.4.2: Scatter-Plot of Levels of Abnormality Per Patient Per Centre (n=86): Systolic Blood Pressure (mmHg)



From Table 13b (Appendix A), following the Kruskal-Wallis tests on the data, there was significant evidence to suggest a treatment difference overall for the number of 'normal' results (p=0.016) and the number of 'high' results (p=0.019). When the data was explored by centre, it was found that there was evidence of a treatment difference for centre 1 only for the number of 'normal' results (p=0.023) and the number of 'high' results (p=0.026).

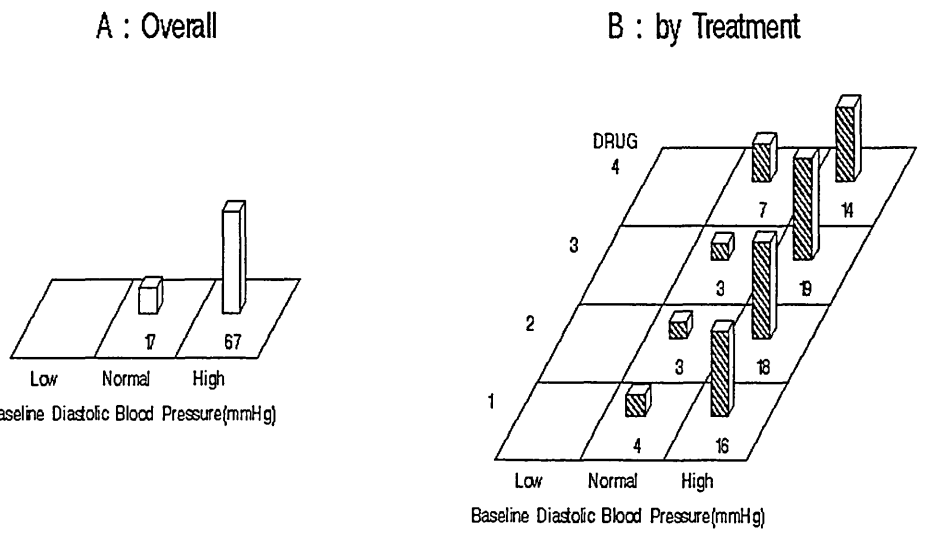
Only 'high' results were of concern for final analysis purposes. Individuals on drugs 1 and 2 had a higher frequency of abnormally 'high' results than individuals on drugs 3 and 4 overall and for centre 1 (see Figure 5.4.2A1).

A chi-squared test was conducted to see whether there was any relationship between the overall frequency of abnormally 'high' readings and treatment group. The findings from Table 14b (Appendix A) shows the distribution of 'high' results and Table 15b shows the chi-squared test results. It can be seen that that there was marginally significant evidence of a treatment difference for the overall data only (p=0.069) and no significant evidence by centre (p>0.143).

From Table 14b (Appendix A), it can be seen that there was a good spread for the frequency of 'high' results. Only 29 individuals had less than or equal to 50% of abnormally 'high' readings. The remaining 57 individuals had more than 50% and 29 of these had greater than 75% of abnormal readings. Chi-squared tests were conducted to see of the frequency of occurrence being > 50% or > 75% was related to treatment groups. The tests were conducted on the overall data and also by centre (Table 16b – Appendix A). In observing the data overall, it was found that only the occurrence of greater than 75% abnormality was significantly different between treatment groups (p=0.025). There was less frequent occurrence for drug 4 than for all other drugs. In looking at the data by centre, it was found that there was only a significant treatment difference for the occurrence of greater than 50% abnormality overall for centre 1 (p=0.048). In this case, drug 4 had only 33.3% of individuals with more than 50% abnormality, whereas 66.7% of the individuals on drug 3, 83.3% of the individuals on drug 1 and 76.9% of the individuals on drug 2 had more than 50% abnormality.

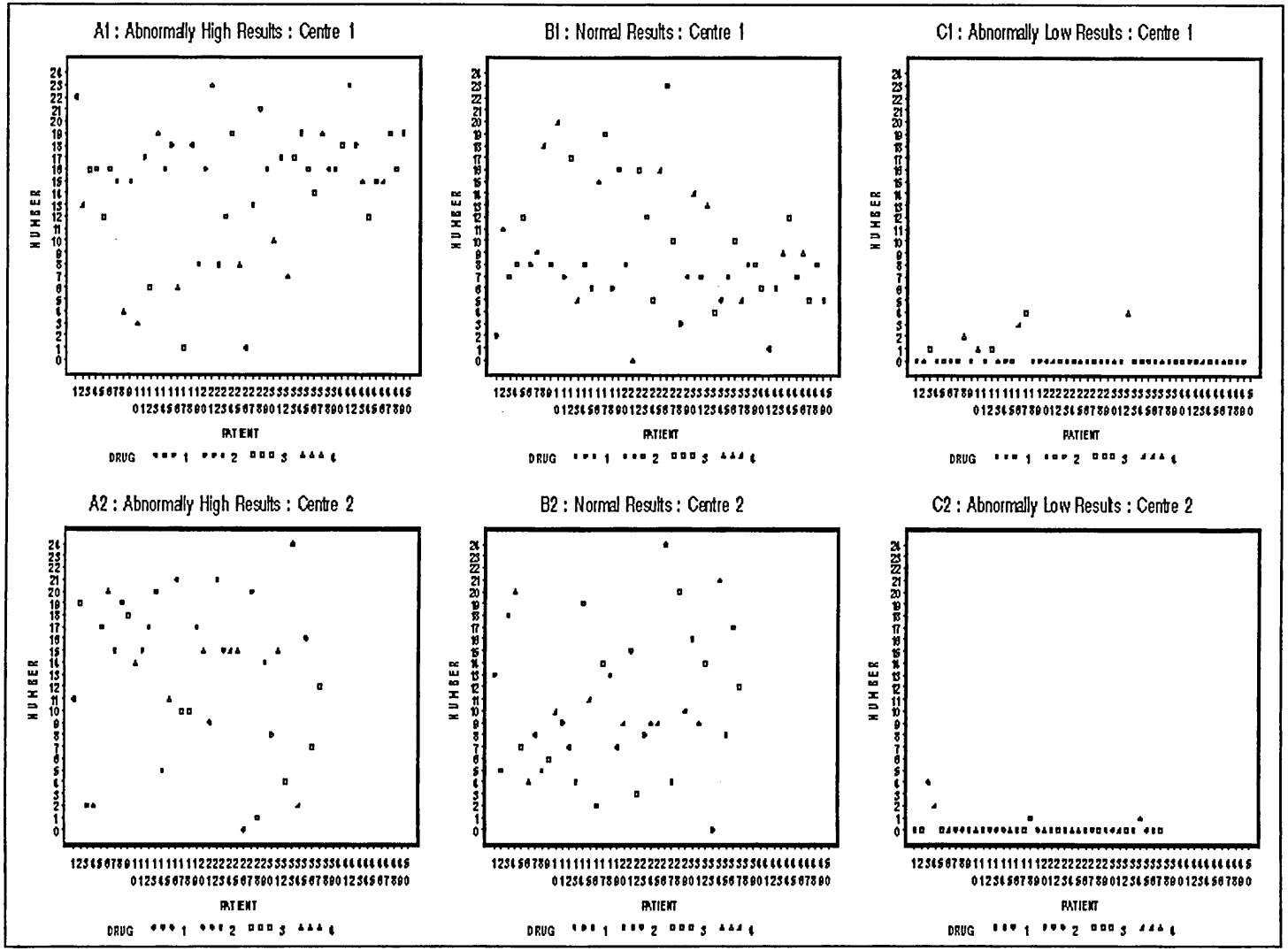
5.2.3: Diastolic Blood Pressure (mmHg)

Figure 5.3.3
Block Charts of Level of Readings for Baseline Diastolic Blood Pressure(mmHg)
Original Data



The data was categorised as being 'low', 'normal' or 'high' at each visit. Figure 5.3.3 above shows that there were no 'low' results at baseline. Only 17 of the 84 individuals with a baseline measurement had a 'normal' result and the remaining 67 had a 'high' baseline response. There was an equal distribution of results across treatment groups. These numbers are identical to those obtained for systolic blood pressure.

Figure 5.4.3: Scatter-Plot of Levels of Abnormality Per Patient Per Centre (n=86): Diastolic Blood Pressure (mmHg)



The total number of on-treatment responses were calculated for 'low' (Figures 5.4.3C1 and 5.4.3C2), 'normal' (Figures 5.4.3B1 and 5.4.3B2) and 'high' (Figures 5.4.3A1 and 5.4.3A2) responses by centre. On looking at the scatter-plots, it can be seen that most of the results for individuals diastolic blood pressure measurements were either 'normal' or 'high'. Only 7 out of 49 individuals in centre 1 and 4 of the 37individuals in centre 2 had at least one 'low' reading. The maximum number of 'low' readings for any individual was 4 in both centres 1 and 2.

From Table 13c, following the Kruskal-Wallis tests (assuming the data was continuous), there was significant evidence to suggest a treatment difference overall for the number of 'low' results ($p=0.025$) only. This was because all treatments apart from drug 2 had at least 1 low response. When the data was explored by centre, it was found that there was only evidence of a treatment difference frequency of 'low' results for centre 1 only ($p=0.034$). Now there were no 'low' results for both drugs 1 and 2.

Only 'high' results were considered to be relevant for final analysis purposes. From Table 14c (Appendix A), it can be seen that the data for the frequency of 'high' results was well distributed. A chi-squared test was conducted to see whether there was any relationship between the frequency of abnormally 'high' readings and treatment groups overall. The findings from Table 15c (Appendix A) show that there was no evidence of any relationship between treatment and frequency of abnormality either by centre or overall ($p>0.179$).

From Table 14c (Appendix A), only 29 individuals had less than or equal to 50% of abnormal readings. The remaining 57 individuals had more than 50% and 18 of these had greater than 75% of abnormal readings. Chi-squared tests were conducted to see of the frequency of occurrence being $> 50\%$ or $> 75\%$ was related to treatment groups. The tests were conducted on the overall data and also by centre (Table 16c-Appendix A). In observing the data, it was found that only the occurrence of greater than 50% abnormality was marginally significant between treatment groups overall ($p=0.062$). All other tests showed no significant relationship between frequency of occurrence and treatment groups ($p>0.080$).

5.3 Overview

It is well known that, under some mild conditions, the summary statistics: sample mean, median, upper quartile and lower quartile are asymptotically normal (jointly or marginally). However, from the extreme value theory, it follows asymptotically that the summary statistics: maximum and minimum (up to their linear transformations) are distributed as Weibull, Frechet or Extreme value random variables. (If V is an exponentially distributed random variable, then V^{α},$V^{-\alpha}$ and log V (where $\alpha > 0$) have respectively Weibull, Frechet and Extreme value distributions).

Our findings in this chapter seem to support the aforementioned results. To examine whether or not there are differences between treatment performances one could appeal to parametric tests such as t (in the case of summary statistic vectors, Hotelling T^2 or Mahalanobis D^2) and likelihood ratio, or non-parametric tests such as Wilcoxon Kruskal-Wallis and homogeneity; when the sample sizes within treatment groups are sufficiently large, then one could still apply the tests to have reasonably reliable conclusions, without insisting that the assumptions of normality be met. The tests that we have applied in the present chapter are among these, and hence our results based on these are of substance. However, one of the major disadvantages of the approach based on summary statistics, considered in this chapter, is the following: The method throws away the information contained in the data on the performances of treatments at various time points; in the case of multidimensional summary statistics the information on the treatment-time interaction is also lost.

As with the univariate data at each time point, it was found that the summary measures data before and after imputing missing data gave similar results for the normality tests, the tests of comparing treatment groups and also for the block charts overall and by treatment group.

The summary measures described in Listings 3.4.1 and 3.4.2 [section 3.3.1] were analysed in both a univariate and multivariate manner. The following chapter 6 will address the details of the analysis in the multidimensional case. An explanation is given of the methods of data reduction applied in order to deal with the multivariate data for multivariate analysis purposes.

CHAPTER 6: Data Reduction

6.0 Introduction

The previous chapter dealt with continuous univariate summary measures that were obtained and analysed using univariate statistical testing. We will now consider the how to analyse the data in a multivariate format. Both Greenhouse and Geisser [27] and Kenward [35] state that while conducting any multivariate modelling methods the number of repeated measurements within a study should be less than the number of patients within a treatment group. This allows the (asymptotic) normality assumptions and hence the model to be approximately valid. The question that we are asking now is what do we do when this condition is not met and hence the normality assumption is not valid?

Reducing the data in some manner would lead to asymptotic normality or to relevant tests that are approximately valid, and, following the theory mentioned in section 2.1.2, it is believed that this would be achieved. Hence the following chapter deals with the various suggested methods of data reduction that could be applied to the continuous longitudinal data sets used for this thesis.

Missing data is usually a problem for multivariate approaches since multivariate analysis is only conducted on individuals with all data available. Again as in the univariate case, normality is a required condition in order for any multivariate statistical testing to be valid. On the other hand, to have the relevant test procedures to be robust, the structure of the data set needs to be such that there are considerably greater number of individuals than the number of repeated measures on each individual. Hence, the various data reduction approaches described below and in section 6.2 were applied to the data and (without loss of generality) an assumption of asymptotic normality was then applied to the data. It was suggested that one of three data reduction methods could be used to set up the data for analysis and allow a more efficient and robust analysis. The three suggested methods of data reduction were:

a) Summary Measures Approach

b) P.C.A.

c) Averaging across time intervals to get segments of time.

The imputation method, used to generate observations for missing records, is described in section 4.2.2. Each of the three reduction methods above were applied to both analysis data sets A and B both before and after imputing missing data and multivariate analyses on all these reduced data formats are carried out in chapter 7. Only the segments of time data (method c above) were analysed using general

univariate methods and the results were compared with those for the original data [section 4.3]. The univariate approach applied to the segments of data is described in chapter 6.

6.1 Multivariate Normality

This is harder to test for than univariate normality. Regression methods could be used to test for normality by regressing y on x or in this case 'RESPONSE' or 'VALUE' on 'TIME' and checking the distribution of the residual or apply some of the methods that have been referred to in chapter 2. However, in the case of our data, we will assume asymptotic normality based on a large sample size [see section 2.1.2]. In order for this assumption to hold, it is suggested that the data across time be reduced using one of the methods given below. This would validate the assumption of normality or the tests used in order for us to proceed with any multivariate analysis methods.

6.2 Reducing the Data Sets

In chapter 2 the reader was introduced to the conditions/assumptions required for conducting most methods of analysis. Most of the parametric methods usually require the assumption of normality of the data. However, it is not always possible to test for normality and in testing the data it is often found that the data are not normally distributed. This is the case especially if the data set were structured such that there were a large number of repeated measures per individual unit. As was stated by Diggle, Liang and Zeger[17], Greenhouse and Geisser [27] and Kenward [35], the problem is that this leads to problems in calculations for any multivariate methods applied to the data. The problems are associated with the calculation of the sums of squares and degrees of freedom (df) for this situation and the condition of normality not being met [section 2.3.2].

If one can not test for and conclude multivariate normality, which is something, that is reasonable to address, then the multivariate tests would require a justification of robustness. For this and in order to satisfy the condition of asymptotic normality [section 2.1.2], to conduct any parametric multivariate approaches, it is suggested that one of three data reduction approaches could be applied to the data to obtain a smaller number of repeated observations.

Most authors then tend to shy away from repeated measures MANOVA in this situation and look for other forms of analysis. For this reason, it has been suggested that rather than shying away from the problem, due to the data not being normal when it has the structure mentioned above, an idea could be put forward of facing the problem head on. The idea is to 'Reduce the Data' using one of three different suggested approaches and then analysing the values in each of the reduced data sets. In applying these

reduction methods, the number of individuals would be considerably greater than the number of repeated measures on each individual. The following three approaches were used to reduce the number of repeated elements in each data set A and B.

Approach 1: Multiple Summary Measures on the Data.

Here a set of 6 summary measures i.e. mean, median, minimum, maximum, lower and upper quartile readings could be calculated and all 6 readings could be analysed together for each individual using a multivariate procedure.

Approach 2: Principal Components Analysis (P.C.A).

This is an extension of the method conducted by Jones and Rice [33] that conducted principal component analysis to reduce the number of individual response measures for ease of analysis. The proposed method here is to use a similar approach, by reducing the repeated measurements instead of reducing the individual profiles.

Approach 3: Using an Averaging Method by Grouping Times at Selected Segments.

The proposed method is to select the number of time points and also the number of individuals within a group and sum up with a proposed number of grouped times that are considered to be appropriate. The method would be to average in-groups of times to come up with a set of grouped time average responses that, while summarising the data, also describe the data at various cross sections over the longitudinal data set.

6.3 Structure of Reduced Multivariate Data

1) Summary Measures (SM)

The six summary statistics (MEAN, MEDIAN, MIN, MAX, Q1 and Q3) mentioned in the previous section were analysed together as one observation. Multivariate vectors of i individuals of 6 readings (or summary statistics) were set up for analysis for each response variable in data sets A and B. Listing 3.4.1 shows the layout of the summary measurements of vital sign measurements for only a few individuals from data set A. A few individual summary measures from data set B are displayed in Listing 3.4.2. These data sets also contain the baseline reading and change of mean from the baseline measurement. These two variables are mentioned later.

2) Principal Components Analysis (P.C.A).

Principal component analysis was conducted on the data sets. In each situation, all components with eigenvalues accounting for approximately 95% of the data were selected for analysis. Multivariate vectors of i individuals by j readings (principal components) were set up for analysis for both data sets A

and B. For the multivariate analysis, there were 10 principal components selected from data set A and only 5 principal components selected from data set B.

3) Averaging over Segments of Time.

We did not wish to test for multivariate normality and hence the idea of reducing the data by averaging across groups of time points was attempted. The assumption of asymptotic normality was met by reducing the data by averaging across groups of times. This was since the number of repeated measures were proportionately less than the number of individuals on whom the measurements were made. The data was split into groups of time points and the mean summary measure was calculated at each of the grouped time points. There were two proposed segmentation methods. The initial method was to average the data in groups of three time points and the second approach was to average across groups of two time points. Data sets A and B were analysed using method 1 and only data set A was analysed using method 2 below. The segmentation methods are detailed below:

Method 1: Averaging over three observations.

A grouped data set was created for both data sets A and B. The 24 on-treatment readings for data set A were reduced to 8 readings and the 9 on-treatment readings for data set B were reduced to 3 readings. Listing 6.1 and Listing 6.2 show the structure of some of the data averaged into groups of 3 times for data sets A and B respectively.

Listing 6.1:Data Set A: After Data Generated: Grouped Data (Average 3 Times): HR(beats/min)

DRUG	PATIENT	GTIME	BASE	AVERAGE OF 3 TIMES
1	10023	1	65.3083	59.750
1	10023	2	65.3083	62.083
1	10023	3	65.3083	64.500
1	10023	4	65.3083	61.333
1	10023	5	65.3083	74.000
1	10023	6	65.3083	71.167
1	10023	7	65.3083	62.500
1	10023	8	65.3083	72.500

continued..

Listing 6.2: Data Set B: After Data Generated:Grouped Data (Average 3): (Dietary Response)

GROUP	SUBJECT	GTIME	BASE	AVERAGE OF 3 TIMES
group1	1	1	1.12598	0.92940
group1	1	2	1.12598	0.97220
group1	1	3	1.12598	1.02080
		continued..		

Method 2: Averaging over two observations.

A grouped data set was created for data set A only since data set B had 9 observations, which were not divisible by 2. For data set A, the 24 on-treatment readings were reduced to 12 readings. Listing 6.3 shows data set A for one individual after averaging across pairs of observations.

Listing 6.3: Data Set A: After Data Generated: Grouped Data (Average 2 Times):Vital Signs

DRUG	PATIENT	GTIME	BASE	AVERAGE OF 2 TIMES
2	10053	1	73.6285	66.500
2	10053	2	73.6285	69.275
2	10053	3	73.6285	70.792
2	10053	4	73.6285	81.350
2	10053	5	73.6285	79.167
		...		
2	10053	11	73.6285	61.750
2	10053	12	73.6285	73.375
		continued..		

6.4 Univariate Methods for Comparison of Reduced Data with Original Data

Of the three approaches that were used to reduce the data, the averaging across time points method was the only approach that still retained a time element. In this chapter, any univariate analyses were only conducted to compare the univariate analysis findings for the data reduced using approach 3 with the univariate analysis findings on the original data. The univariate analyses conducted on the reduced data were:

a) Individual profile plots over grouped times.

b)Mean, Median, Minimum and Maximum plots over grouped times.

c) Univariate Kruskal-Wallis tests to compare treatments per grouped time for the reduced data using segmentation.

d) Block chart of the summary measure of mean change from baseline.

e) Univariate Kruskal-Wallis tests to compare treatments for summary measures overall and by centre for reduced data using segmentation.

All univariate analysis methods mentioned above were conducted on the reduced data using approach 3 both before and after generating missing records. However, since there were no vast differences in the results before and after generating missing data, only the results on the data after generating missing records are displayed in this thesis.

The univariate plots (a) and (b) were produced to show the individual profiles and summary measures for the reduced data over each time segment. The block chart (d) showed an overall summary of the data per treatment group and overall.

Following the methods of data reduction using method 1, there were only 8 on-treatment measures in place of the 24 for vital sign data and 3 observations instead of 9 for the dietary response data. Following method 2, there was a set of 12 on-treatment-repeated measurements instead of 24 initial measurements for the vital signs data only. This second approach was not applied to the dietary response data set.

6.5 Univariate Analysis for Each Reduced Data Point

The purposes of these analyses were to compare the methods conducted on the reduced data after imputing missing data using data reduction approach 3 with those conducted on the original data before reduction of the time points and see if the trends in the data were maintained.

6.5.1: Individual Profile Plots.

Plots of the individual response profiles were produced for the reduced data by averaging over grouped time points. Only figures on the reduced data after imputing missing readings are displayed below. Figures 6.1.1 to 6.1.4 show respective individual profile plots for heart rate, systolic and diastolic BP and dietary response for method 1. Figures 6.2.1 to 6.2.3 show the respective individual profile plots for method 2 for vital signs data only. Profile plots were produced separately per treatment group. The trends in the data could be seen but these plots were not very useful otherwise. There was, as expected, far too much variation in individual responses. It was found that reducing the data, by averaging across segments of time, gave a similar picture to the original data. Any fluctuations in the data were smoothed

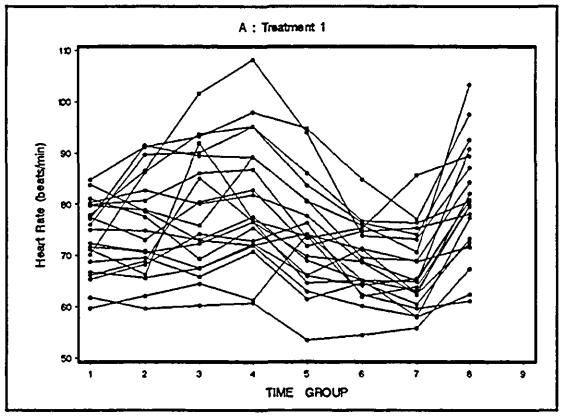
out after the process of averaging across segments of time points. Individual differences became more obvious as more time elements were used in the segmentation process.

6.5.1.1 Heart Rate (beats/min):

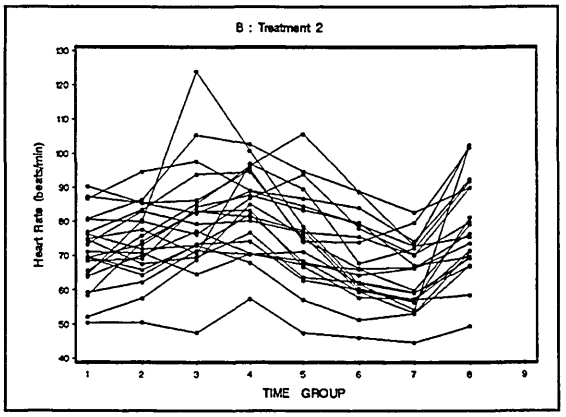
Method 1: Averaging Over Three Time Points

FIGURE 6.1.1
Patient Profiles of Heart Rate (b/m) By Treatment After Averaging Over ThreeTime Points

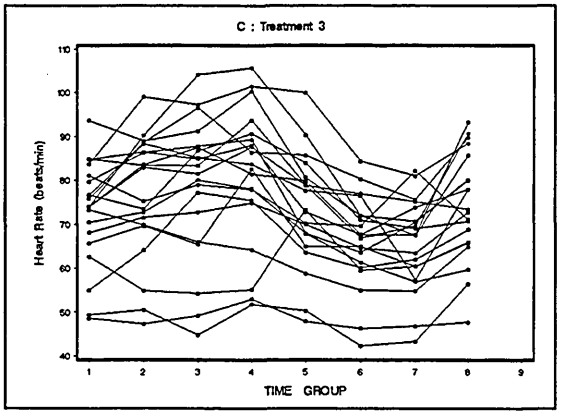
A : Treatment 1



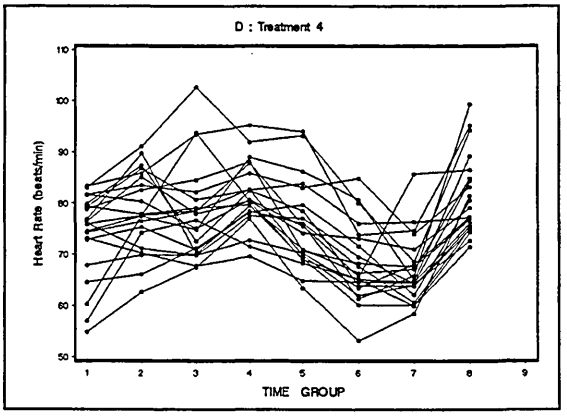
B : Treatment 2



C : Treatment 3



D : Treatment 4

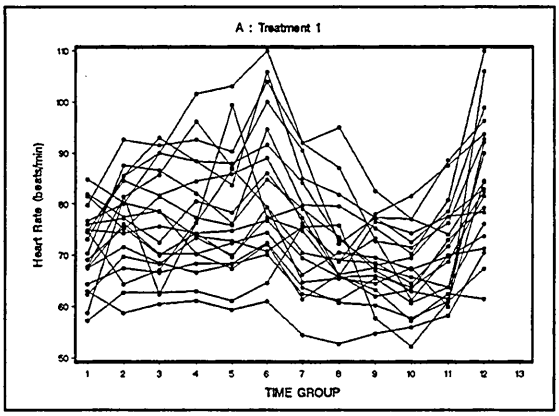


Using method 1 (Figures 6.1.1A to D) it can be seen that, for all four drugs, the data peaks around grouped times 3 or 4 (original time 7 or 12) and dips at grouped time 7 (original times 19 to 21). The data finally peaks again at grouped time 8 (original times 22 to 24).

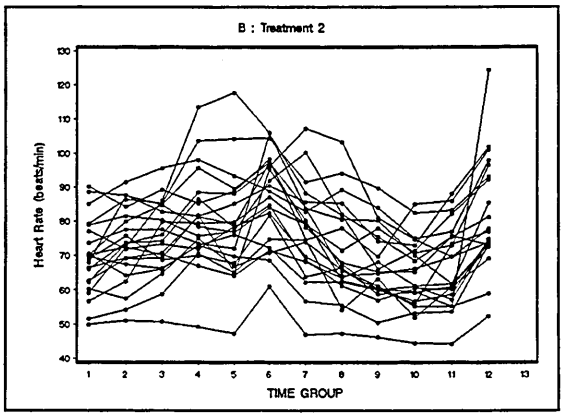
Method 2: Averaging Over Two Time Points

FIGURE 6.2.1
Patient Profiles of Heart Rate (b/m) By Treatment After Averaging Over TwoTime Points.

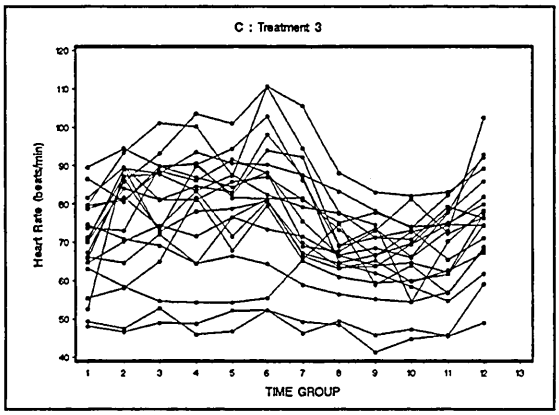
A : Treatment 1



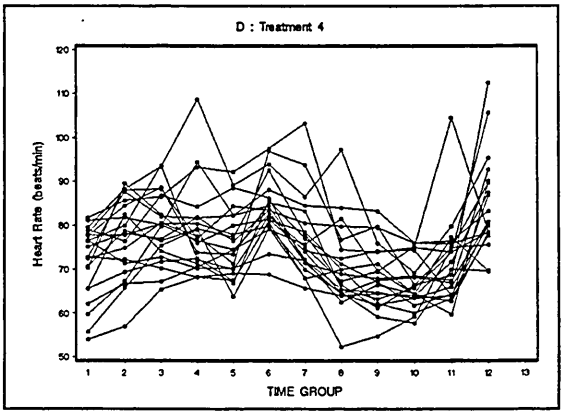
B : Treatment 2



C : Treatment 3



D : Treatment 4



Similar results to method 1 were found using method 2 (Figures 6.2.1A to D) where it can be seen that the data peaks at around grouped times 4 or 6 (7-12 hours), dips around grouped time 10 (19-20 hours) and peaks again at grouped time 12 (23-24 hours).

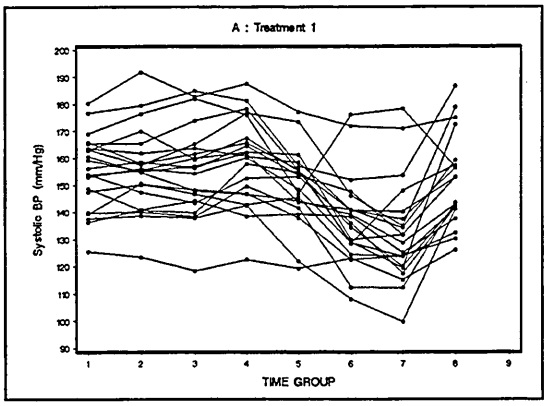
Both reduction methods 1 and 2 above agree with the results obtained for the original data set before missing data was replaced (Figures 4.1.1 A to D). Notice, however, that fluctuations in the data are smoothed out after the process of averaging across segments of time points. Individual differences became more obvious as more time elements were used in the segmentation approach.

6.5.1.2 Systolic BP (mmHg).

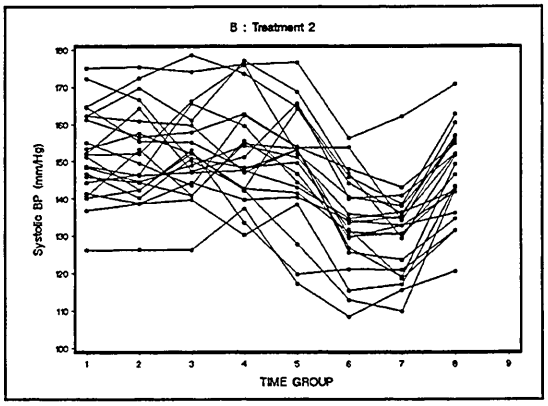
Method 1: Averaging Over Three Time Points

FIGURE 6.1.2
Patient Profiles of Systolic BP (mmHg) By Treatment After Averaging Over Three Time Points.

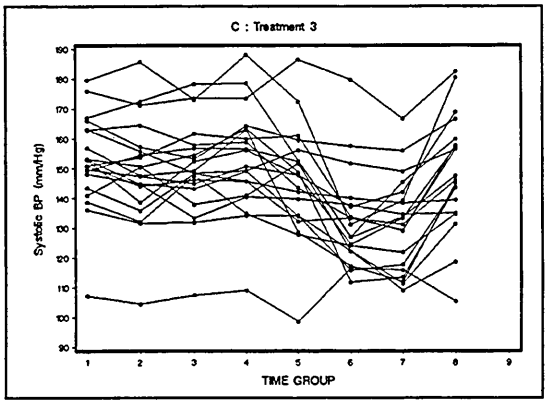
A : Treatment 1



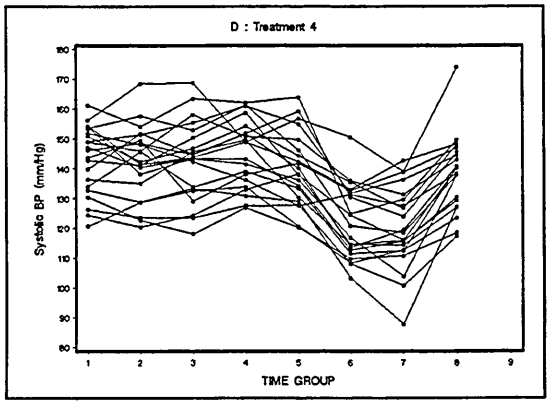
B : Treatment 2



C : Treatment 3



D : Treatment 4

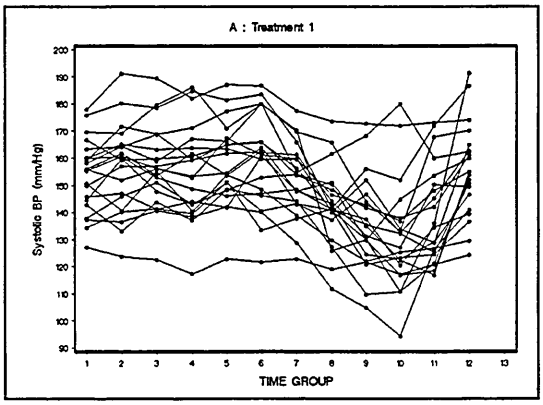


The individual profile plots using methods 1 (Figures 6.1.2A to D) seemed to show that almost all individuals had a drop in systolic BP at around grouped time 7 (original times 19 to 21). One individual on drug 1 and an individual on drug 3 had considerably lower readings than all other individuals indicating outlying values.

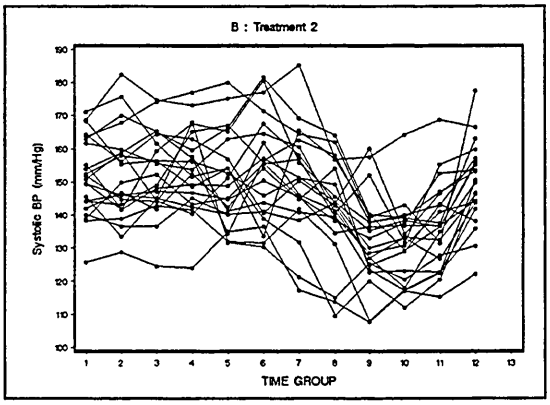
Method 2: Averaging Over Two Time Points

FIGURE 6.2.2
Patient Profiles of Systolic BP (mmHg) By Treatment After Averaging Over Two Time Points.

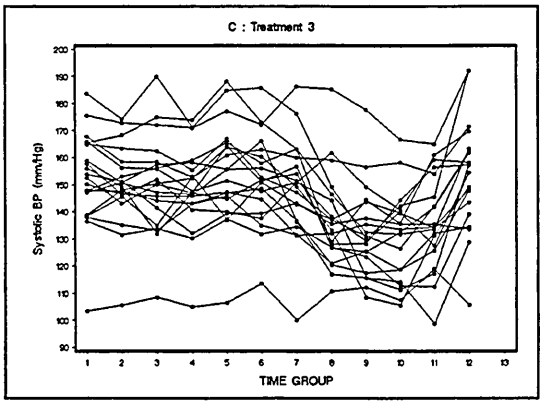
A : Treatment 1



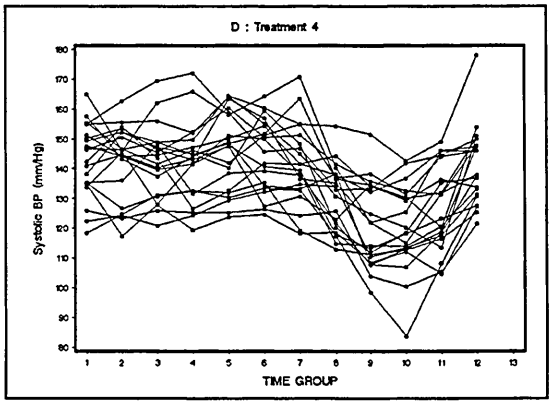
B : Treatment 2



C : Treatment 3



D : Treatment 4



The individual profile plots Figures 6.2.2 A to D above were produced using method 2. One individual on both drug 1 and 3 had considerably lower readings than any other individuals. The data tended to drop at about grouped times 10 or 11 (original times 19 to 22).

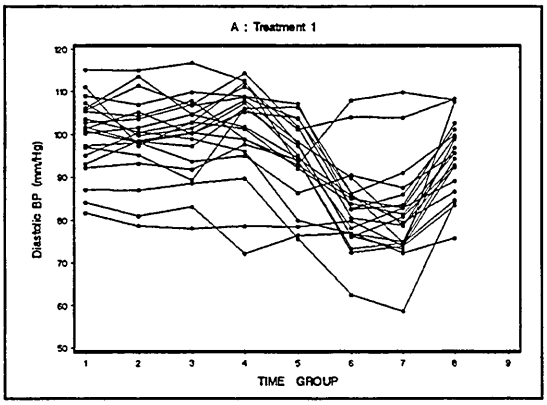
Both methods 1 and methods 2 above lead to similar findings, as were also observed for the original data in Figures 4.1.2 A to D. Notice that fluctuations in the data are smoothed out after the process of averaging across segments of time points. Individual differences became more obvious as more time elements were used in the segmentation approach.

6.5.1.3 Diastolic BP (mmHg).

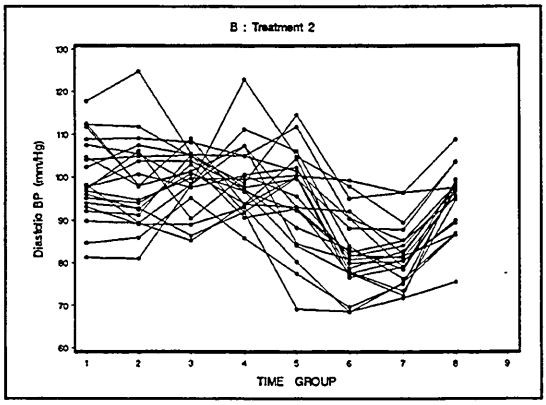
Method 1: Averaging Over Three Time Points

FIGURE 6.1.3
Patient Profiles of Diastolic BP (mmHg) By Treatment After Averaging Over Three Time Points.

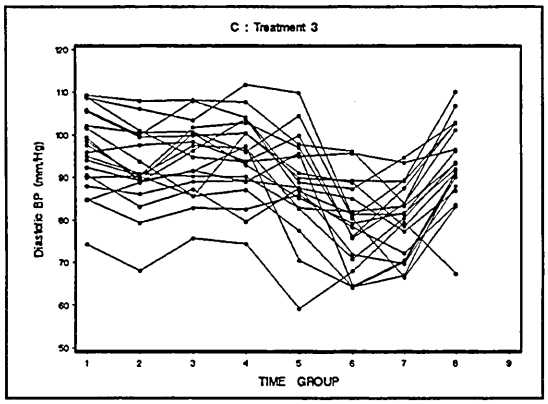
A : Treatment 1



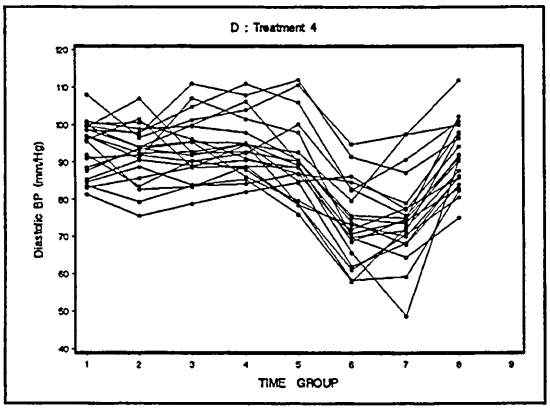
B : Treatment 2



C : Treatment 3



D : Treatment 4

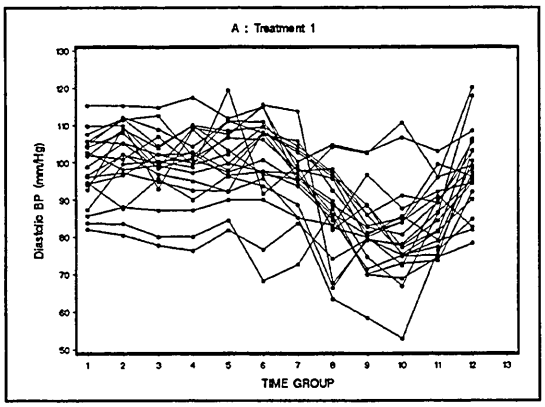


The individual profile plots Figures 6.1.3 A to D above were produced using method 1. In all cases, the data tended to drop at about grouped times 6 or 7 (original times 16 to 21). These plots are very cluttered and difficult to interpret.

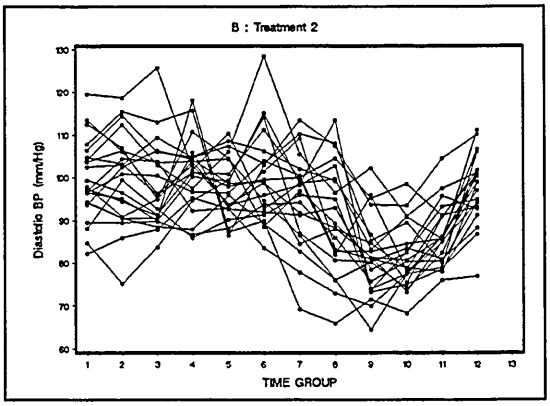
Method 2: Averaging Over TwoTime Points

FIGURE 6.2.3
Patient Profiles of Diastolic BP (mmHg) By Treatment After Averaging Over Two Time Points.

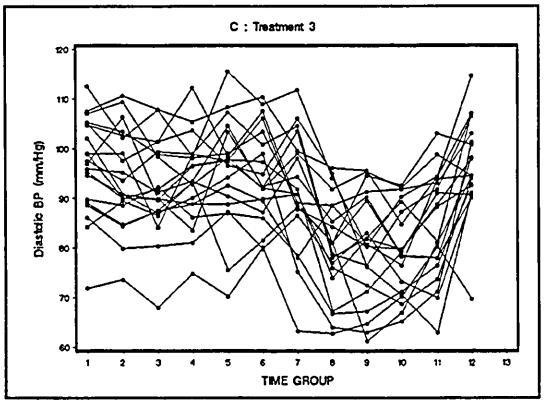
A : Treatment 1



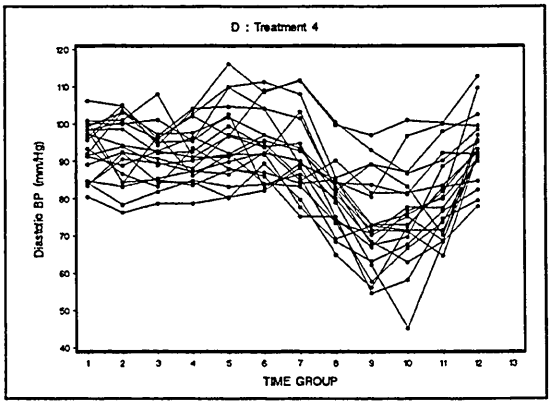
B : Treatment 2



C : Treatment 3



D : Treatment 4



The individual profile plots Figures 6.2.3 A to D above were produced using method 2. In all cases, the average diastolic blood pressure data tended to drop at about grouped times 9 or 10 (original times 17 to 20).

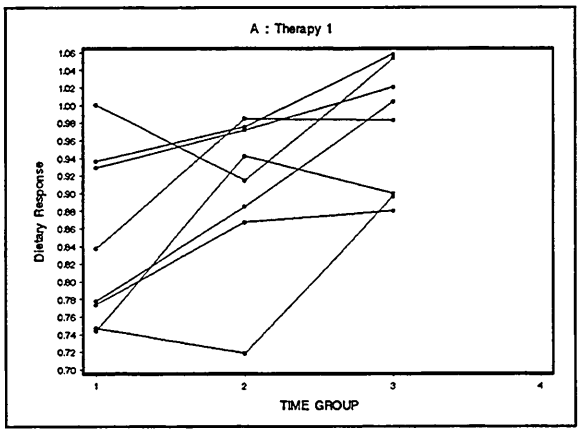
The individual profile plots using methods 1 (Figures 6.1.3A to D) and a method 2 (Figures 6.2.3A to D) were similar in appearance to the original data plots (Figures 4.1.3A to D). Fluctuations in the data became smoother after the averaging process across segments of data. Individual differences became more obvious as more time elements were used in the segmentation approach.

6.5.1.4 Dietary Response.

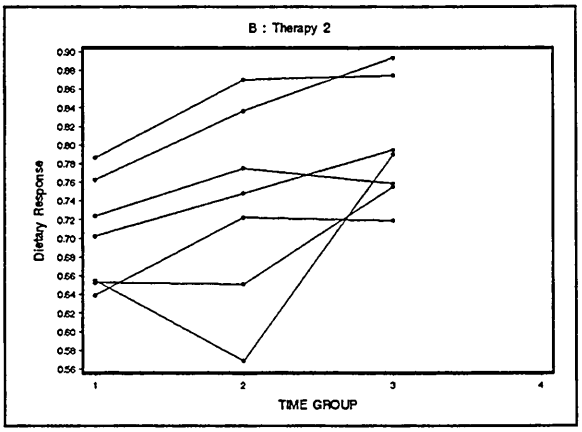
Method 1: Averaging Over Three Time Points

FIGURE 6.1.4
Patient Profiles of Dietary Response By Therapy After Averaging Over Three Time Points. After Missing Data Replaced (N=24).

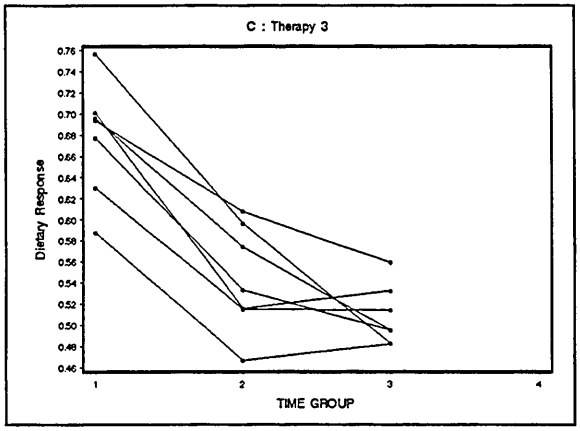
A : Therapy 1



B : Therapy 2



C : Therapy 3



Figures 6.1.4A to C describe the reduced individual profile data using method 1. Therapy 1 and 2 appeared to have an increasing linear trend with time and therapy 3 had a decreasing linear trend with time. Data reduction on the dietary response data was not conducted using method 2. The findings on the reduced data using method 1 agree with those on the original data in Figures 4.1.4A to C.

Note: The fluctuations in the data were reduced following the data reduction approach.

6.5.2: Summary Response Profile Plots.

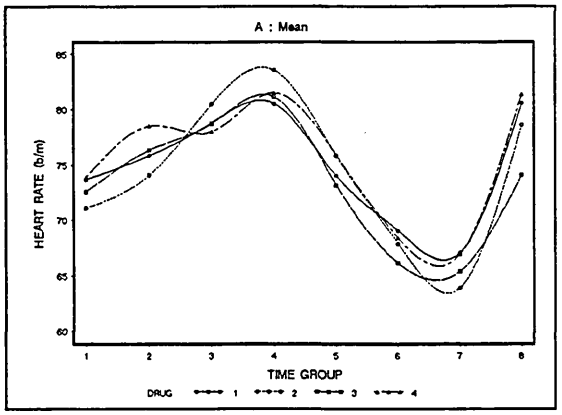
Only figures on the reduced data following the imputing of missing readings are displayed. The summary response profiles for the mean, median, minimum and maximum response were produced for the reduced data using both method 1 (Figures 6.3.1A-D to 6.3.3A-D) and method 2 (Figures 6.4.1A-D to 6.4.3A-D) for the vital signs data. For the dietary response data, summary response profile plots were produced using only method 1 (Figures 6.3.4A to D).

6.5.2.1 Heart Rate (beats/min).

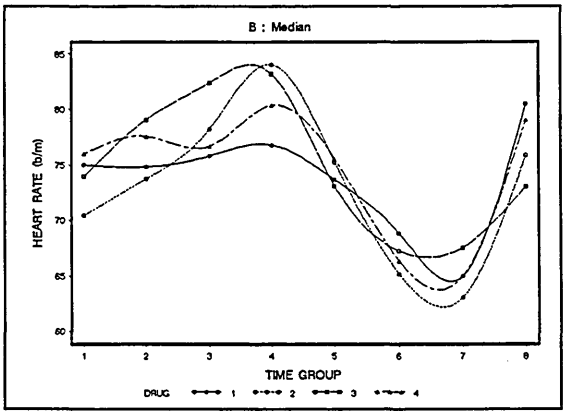
Method 1: Averaging Over Three Time Points

FIGURE 6.3.1
Plots of Summary Response Profiles by Treatment Group After Averaging Over Three Times For Heart Rate(b/m): After Missing Data Replaced (N=86).

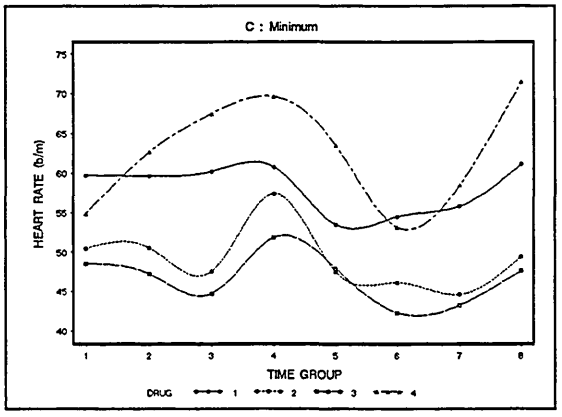
A : Mean



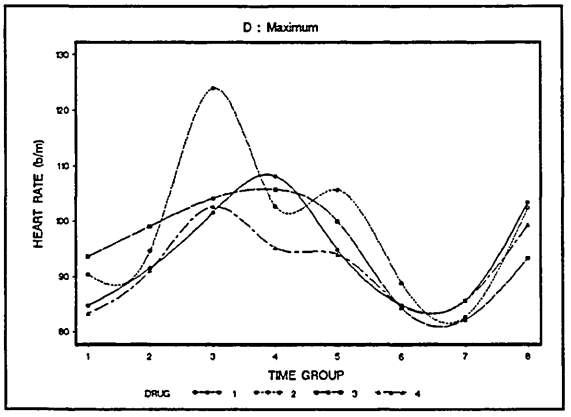
B : Median



C : Minimum



D : Maximum



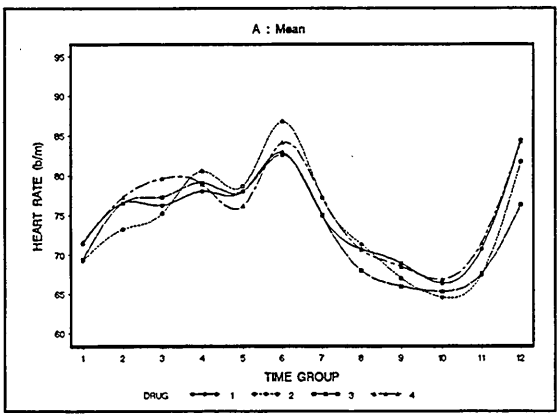
The mean plot using method 1 (Figure 6.3.1A) shows a peak at grouped times 4 (10-12 hours) and 8 (22-24 hours) and a drop at grouped time 7 (19-21 hours). The median plots (Figures 6.3.1B) show similar patterns in the data but there is more variation between treatment groups up to the initial peak of grouped time 4 (10-12 hours). The data then behaves similarly from that point on. Drug 2 has both the lowest mean and median heart rate response at grouped time 7 (19-21 hours). The minimum plot (Figures

6.3.1C) shows much variation between treatment groups especially between drugs 3 and 4. The maximum plot (Figure 6.3.1D) indicates that there is an extreme value at grouped time 3 (original time 9) for drug 2. This is confirmed in the maximum plot for the original data in Figure 4.3.1D.

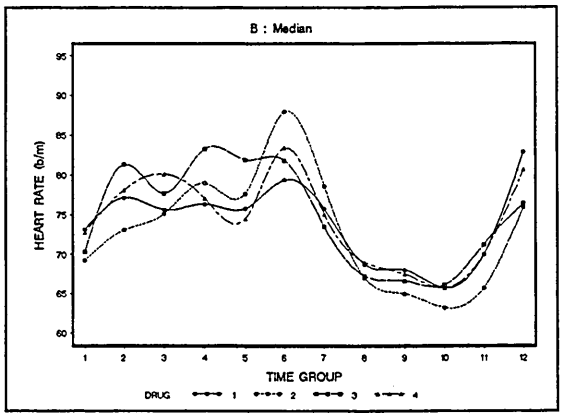
Method 2: Averaging Over Two Time Points

FIGURE 6.4.1
Plots of Summary Response Profiles by Treatment Group After Averaging Over Two Times For Heart Rate(b/m): After Missing Data Replaced (N=86).

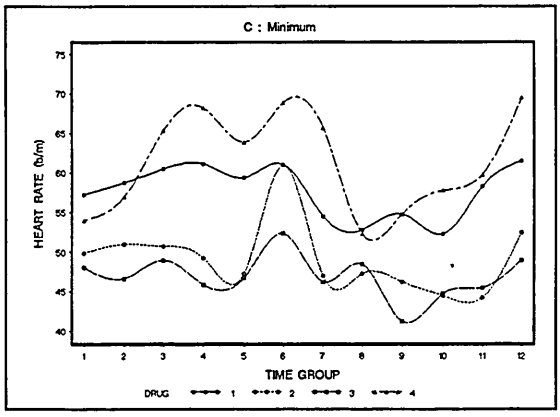
A : Mean



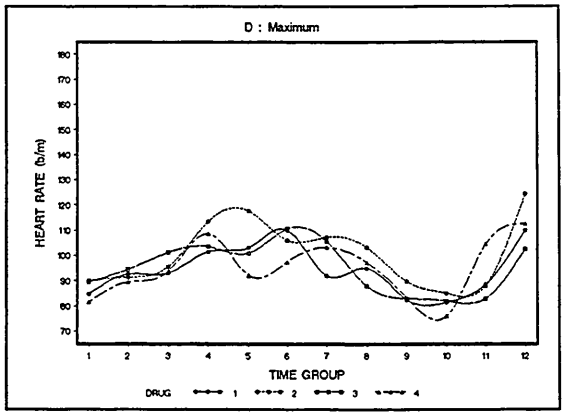
B : Median



C : Minimum



D : Maximum



The mean plot for method 2 (Figure 6.4.1A) shows a peak at grouped time 6 (11 to 12 hours) and 12 (23 to 24 hours). The median plots using method 2 (Figures 6.4.1B) show similar patterns to the mean plot (Figure 6.3.1A) but there is more variation between treatment groups for the median plot. Drug 2 has both the largest median response at grouped time 6 (11-12 hours) and the lowest median response from grouped time 8 (15-16 hours) onwards. Again the minimum plot (Figure 6.4.1C) shows much more treatment variation.

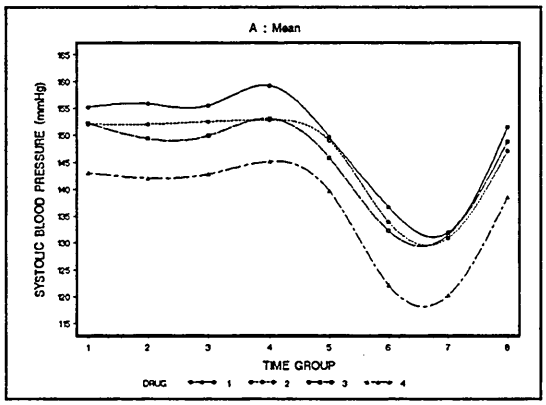
Both reduction methods agree with results obtained from the original plots (Figures 4.3.1A-D). All mean plots show the data behaves in a similar pattern for all four therapies with the mean data being close together. All methods show no vast treatment differences in the mean.

6.5.2.2 Systolic BP (mmHg).

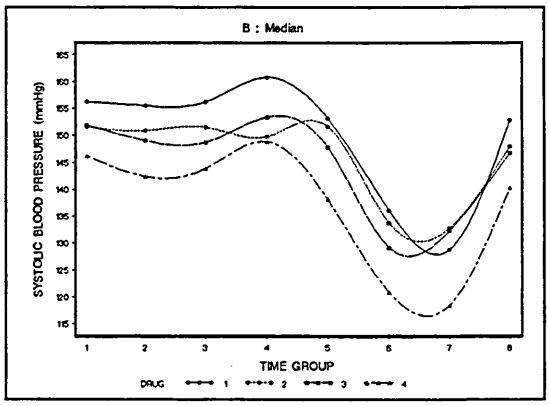
Method 1: Averaging Over Three Time Points

FIGURE 6.3.2
Summary Profiles By Treatment After Averaging Over Three Times For Systolic BP (mmHg)

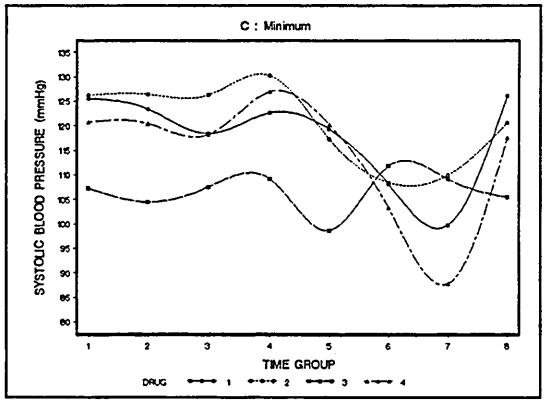
A : Mean



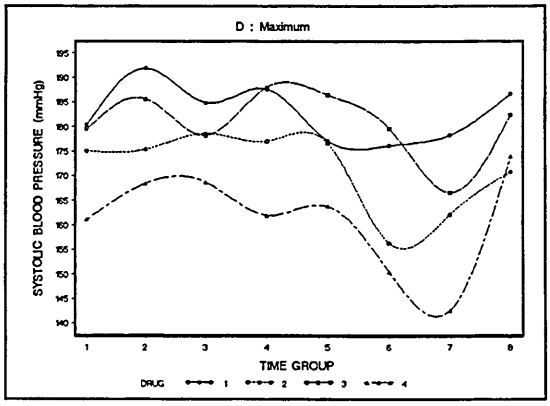
B : Median



C : Minimum



D : Maximum



Figures 6.3.2A to D show the mean, median, minimum and maximum plots across time by treatment groups for data reduction using segmentation method 1. The mean plot for all drugs using data reduction method 1 (Figure 6.3.2A) shows a peak at grouped time 4 (10-12 hours). The data stays approximately constant before grouped time 4, where it peaks and then immediately drops until grouped time 7 (19-21 hours) and then suddenly increases at grouped time 8 (22-24 hours). Drug 1 has the largest mean responses for most time points following data reduction method 1.

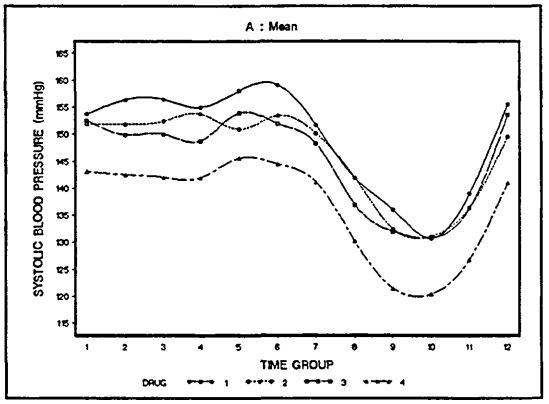
It can be seen that there is a difference in mean, median and maximum response with drug 4 having considerably lower readings than the other treatment groups. The minimum response for drug 3 is considerably lower than for the other treatment groups up to grouped time 6 (16 to 18 hours) for method 1. After this time drug 4 has the lowest readings.

Method 2: Averaging Over Two Time Points

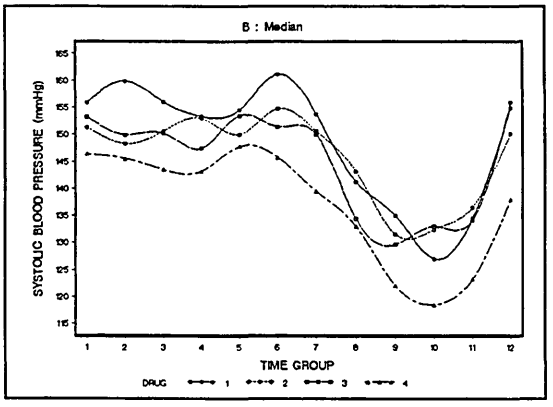
FIGURE 6.4.2

Summary Profiles by Treatment Group After Averaging Over Two Times For Systolic BP

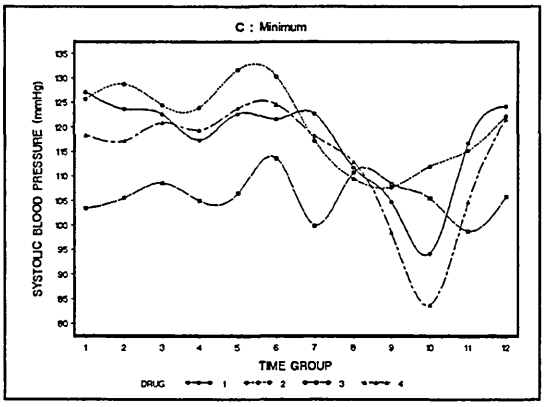
A : Mean



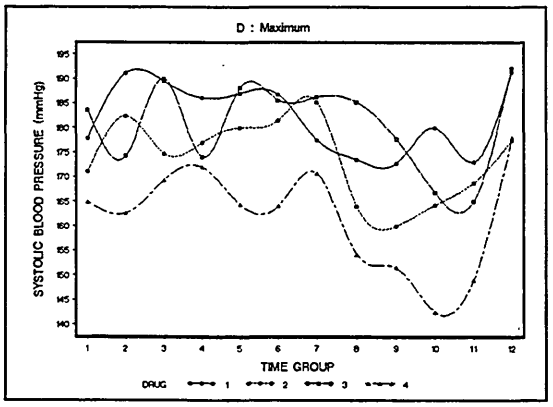
B : Median



C : Minimum



D : Maximum



The mean, median, minimum and maximum plots for method 2 (Figures 6.4.2A to D) show a similar pattern to the plots for method 1 (Figures 6.3.2A to D) and for the original data (Figures 4.3.2A to D). Following data reduction using method 2, drug 4 had the lowest mean (Figure 6.4.2A), median (Figure 6.4.2B) and maximum (Figure 6.4.2C) systolic BP response over all grouped times. Drug 1 has the largest mean responses for all grouped time points following data reduction method 2.

The general patterns in the original data are maintained by data reduction through segmentation.

All reduction method plots show a similar picture to the plots produced for the original data (Figures 4.3.2A to D). As the data become further reduced by data segmentation, it can be seen that the fluctuations in the data become smoother. Differences in the data become more obvious within the plots as more time points are used in the reduction process.

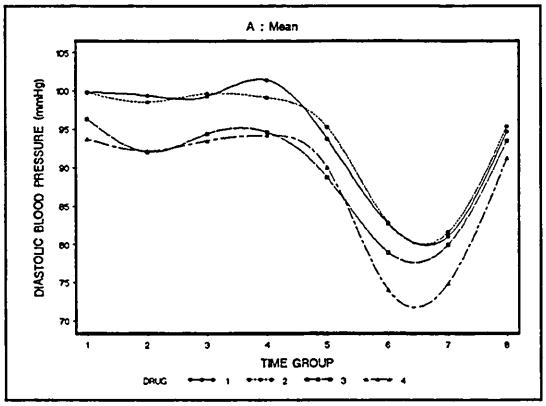
6.5.2.3 Diastolic BP (mmHg).

Method 1: Averaging Over Three Time Points

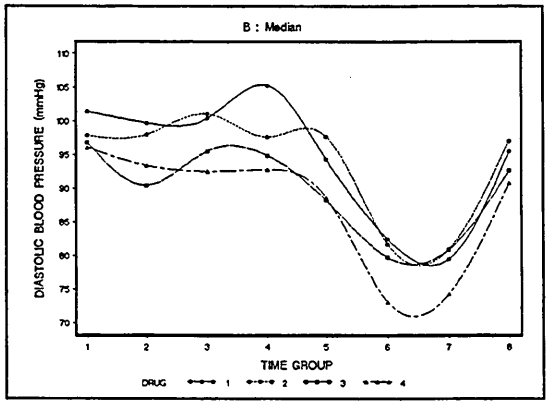
FIGURE 6.3.3

Summary Profiles By Treatment After Averaging Over Three Times For Diastolic BP (mmHg)

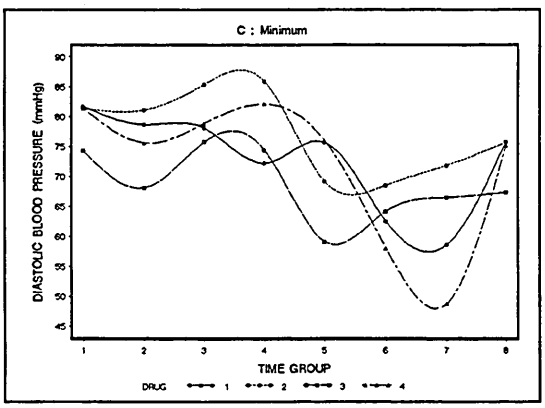
A : Mean



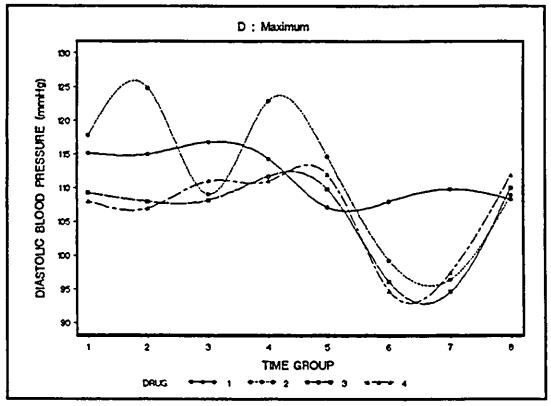
B : Median



C : Minimum



D : Maximum



Figures 6.3.3 A to D show the respective mean, median, minimum and maximum diastolic blood pressure plots across time by treatment groups for segmentation data reduction method 1.

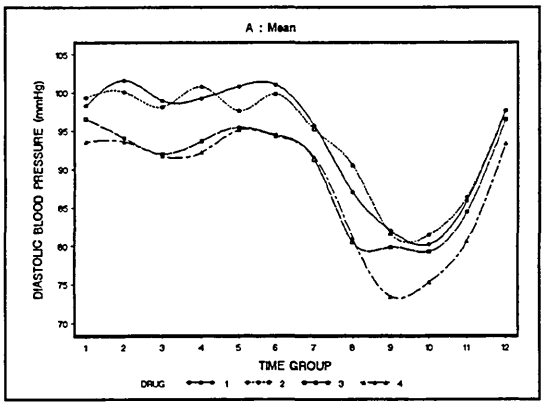
Drug 4 has lower mean responses than all other treatments at most of the grouped times apart from grouped time 5 (13 to 15 hours) using method 1. Drugs 1 and 2 had higher mean and median responses over the grouped time points compared with drugs 3 and 4.

Method 2: Averaging Over Two Time Points

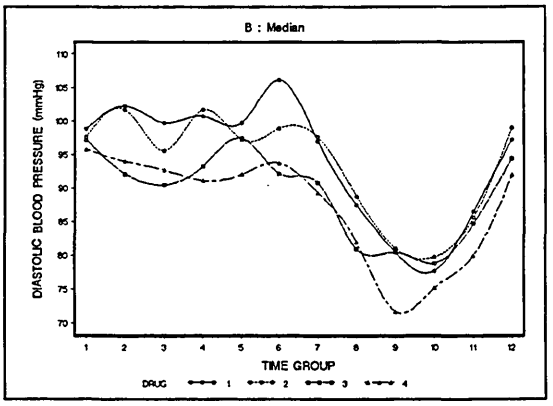
FIGURE 6.4.3

Summary Profiles by Treatment Group After Averaging Over Two Times For Diastolic BP

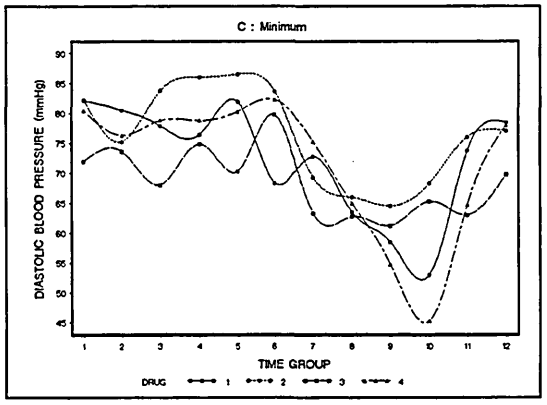
A : Mean



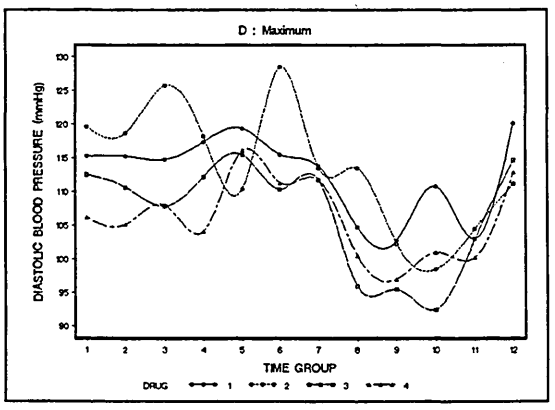
B : Median



C : Minimum



D : Maximum



Figures 6.4.3 A to D show the respective mean, median, minimum and maximum diastolic BP plots across time by treatment groups for data reduction method 2. The plots show similar patterns to the plots for the data using method 1 (Figures 6.3.3A to D) and the original data plots (Figures 4.3.3A to D). Obvious differences in treatment were noticed between drugs 1 and 4, with drug 4 having lower responses and drug 1 having higher responses.

The general patterns in the original data were maintained through data reduction. The average diastolic blood pressure data varied in a similar pattern to the systolic blood pressure. In other words, times of peaks and troughs in the data were consistent for both systolic BP and diastolic BP measurements. There seem to be larger overall differences in the average responses for treatments at the initial times compared to the times later on in the study. Drug 4 had obviously lower mean and median readings after

grouped time 6 (16-18 hours) for method 1 and grouped time 8 (15-16 hours) for method 2. This agrees with the findings on the original data after time 16 hours.

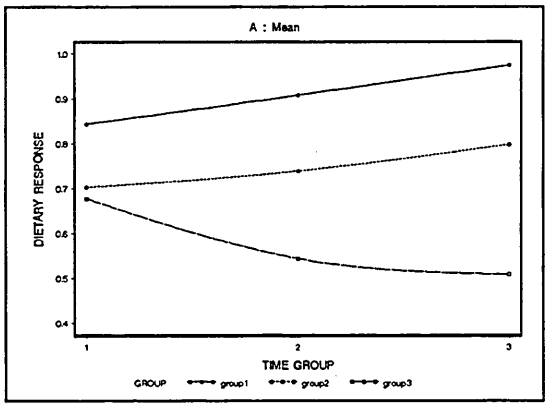
6.5.2.4 Dietary Response.

Method 1: Averaging Over Three Time Points

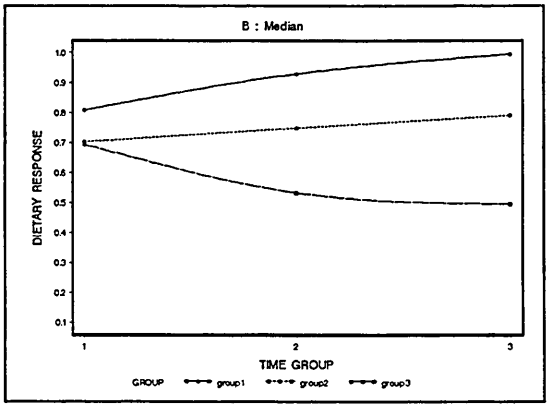
FIGURE 6.3.4

Summary Profiles By Treatment After Averaging Over Three Times For Dietary Response

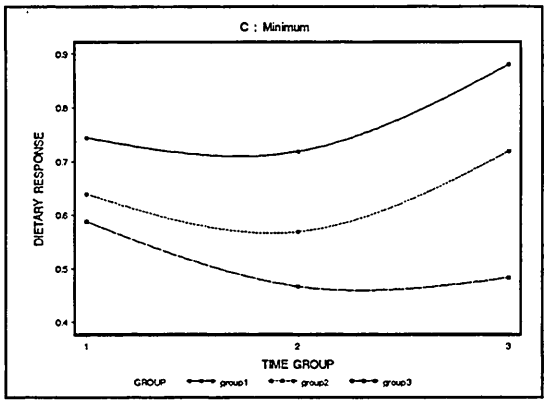
A : Mean



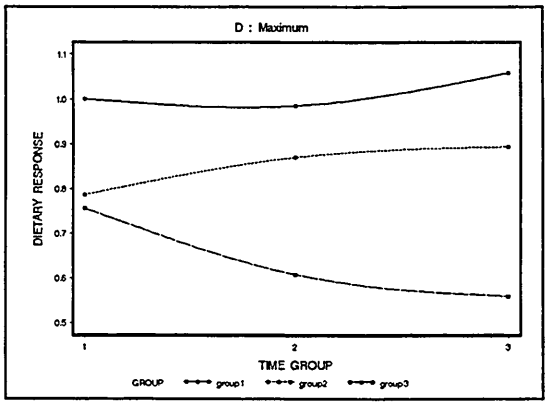
B : Median



C : Minimum



D : Maximum



From Figures 6.3.4A to D, it can be seen that the data are now almost linear in appearance. There are obvious treatment differences between all three-therapy groups following data reduction using method 1 (Figures 6.3.4.A to 6.3.4D). The differences are similar to those seen for the original data before data reduction (Figures 4.3.4A to D). Therapy 1 has higher mean, median, minimum and maximum readings than therapy 2, which has higher readings than therapy 3. The mean and median differences are highlighted further along in time.

6.5.3: Univariate Testing.

The segmentation methods for data reduction were applied to the data before and after imputing the data. The data gave similar results before and after imputing missing information. Hence, only the results for the reduced data after replacing missing information are displayed. Univariate normal and Kruskal-Wallis tests were conducted to test for the distribution of the data and also test for treatment differences. The Kruskal-Wallis Test was conducted on the data at each univariate reduced time point.

For data reduction using segmentation, both methods 1 and 2 were applied to all vital sign data (heart rate, systolic blood pressure and diastolic blood pressure). Only method 1 was applied to the dietary response data. There is no other purpose to these tests apart from to compare the results obtained on the reduced data with those obtained on the original data before imputing missing data.

6.5.3.1 Heart Rate (beats/min).

The univariate Kruskal-Wallis tests for each grouped time using method 1 ($p>0.169$, Table 3a – Appendix A) show no treatment differences, as do the tests using method 2 ($p>0.126$, Table 4a – Appendix A). Both results agree with one another and also with those obtained on the original data (Table 4.2.1) for the univariate tests over time.

6.5.3.2 Systolic Blood Pressure (mmHg)

The univariate tests for each grouped time for the data from method 1 (Table 3b –Appendix A) showed treatment differences at grouped times 1, 2, 3, 4, 6 and 8. The tests on the data from method 2 (Table 4b – Appendix A) showed treatment differences at times 1, 2, 3, 4, 6, 8, 9 and 12. Both results seem to agree with the results obtained from the univariate tests on the original data (Table 4.2.2) where treatment differences were found at times 1, 3, 5, 6, 7, 8 16, 17, 18, 19, 21, 23 and 24 hours.

6.5.3.3 Diastolic Blood Pressure (mmHg)

Univariate tests for the grouped time point for the data using method 1 (Table 3c – Appendix A) showed there to be treatment differences at grouped times 2, 3, 4 and 6. The tests on the data from method 2 (Table 4c – Appendix A) showed treatment differences at grouped times 2, 3, 4, 6, and 8. Both results agree with the results obtained from the univariate tests on the original data (Table 4.2.3) where treatment differences were found at times 3, 5, 6, 7, 8, 10, 11, 16 and 21 hours.

6.5.3.4 Dietary Response.

Significant differences were noted at all reduced time points ($p<=0.003$) using method 1 (Table 3d – Appendix A). This agrees with the findings from the original data (Table 4.2.4), where significant treatment differences were found at times 2, 3, 4, 5, 6, 7, 8 and 9.

6.6 Univariate Summary Measures for Reduced Data

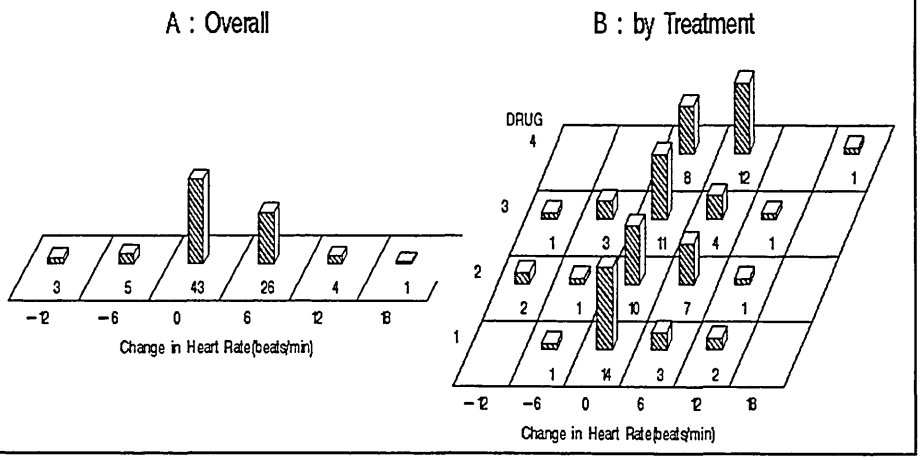
6.6.1: Distribution of the Change in Mean from Baseline.

A block chart of the overall and by treatment change of 'on-treatment' mean from baseline response across time was produced for the data. Only figures on the reduced data after imputing missing readings are displayed. Both normality and univariate Kruskal-Wallis tests on the change in mean from baseline were conducted for the reduced imputed data. These results were compared with the corresponding findings for the original data before data replacement.

6.6.1.1 Heart Rate (beats/min)

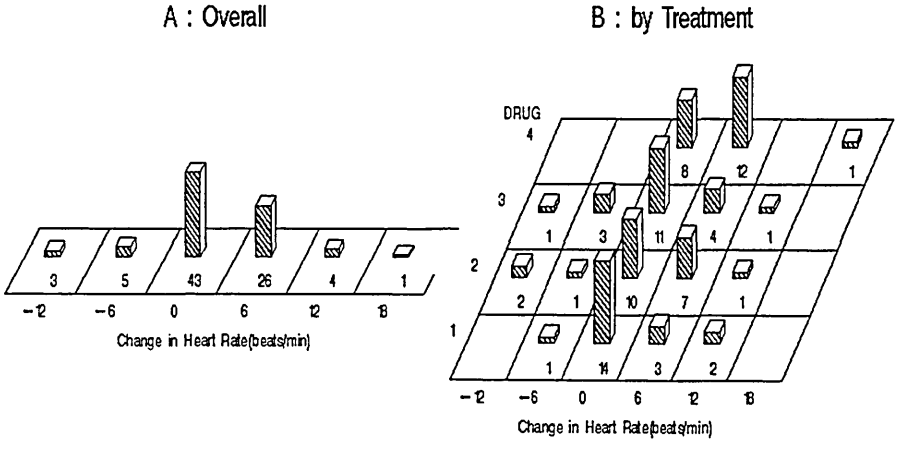
Method 1: Averaging Over Three Time Points

Figure 6.5.1
Block Charts of Change in Heart Rate(beats/min) Values : Average of 3 Time Points



Method 2: Averaging Over Two Time Points

Figure 6.6.1
Block Charts of Change in Heart Rate(beats/min) Values : Average of 2 Time Points

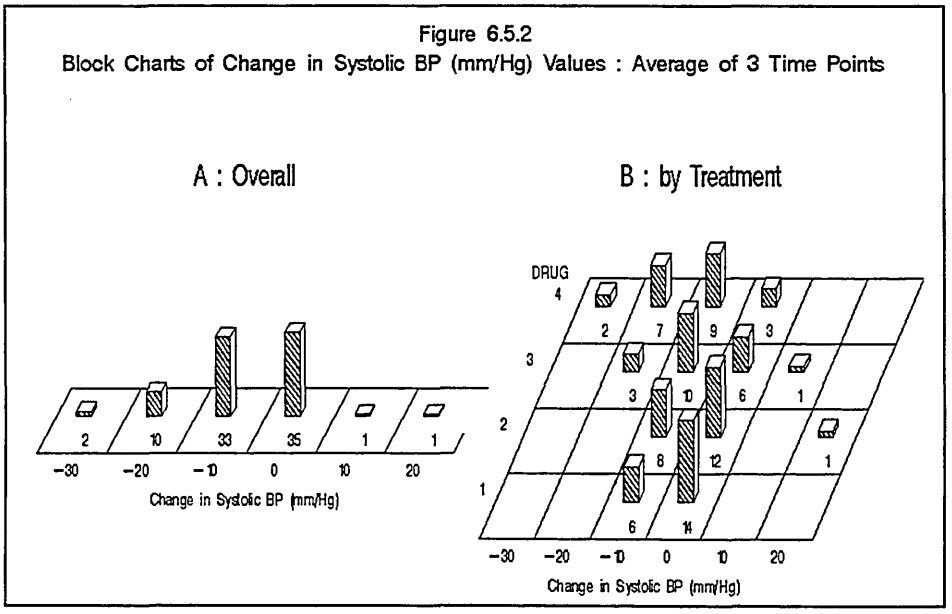


For the change in the mean from baseline for method 1 (Figures 6.5.1A and B and Tables 8a – Appendix A) and for method 2 (Figures 6.6.1A and B and Tables 10a – Appendix A) the findings agree with the results for the original data (Figures 5.1.1B and 5.2.1B and Table 5.1.1). Both figures for methods 1 and 2 were identical. It can be seen that one individual on drug 4 is an outlier with a reading between 15 to 21 whereas all other results appear to range from –15 to 15. It can also be seen that all therapy groups apart from drug 3 appeared to have a skewed distribution. The normal tests in Tables 8a (Appendix A) for method 1 and Table 10a (Appendix A) for method 2 confirm this statement. There are no treatment differences for the change in mean from baseline for both methods 1 and 2 (p=0.173 for both).

6.6.1.2 Systolic BP (mmHg).

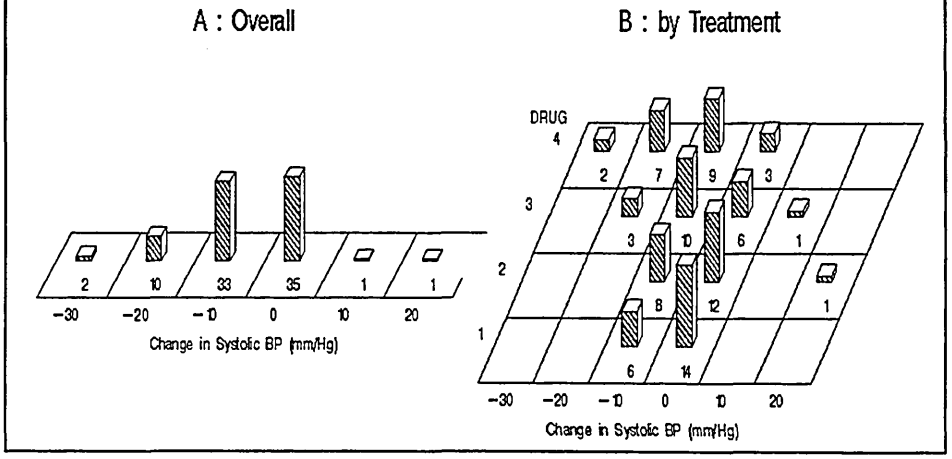
Method 1: Averaging Over Three Time Points

Figure 6.5.2
Block Charts of Change in Systolic BP (mm/Hg) Values : Average of 3 Time Points



Method 2: Averaging Over Two Time Points

Figure 6.6.2
Block Charts of Change in Systolic BP (mm/Hg) Values : Average of 2 Time Points

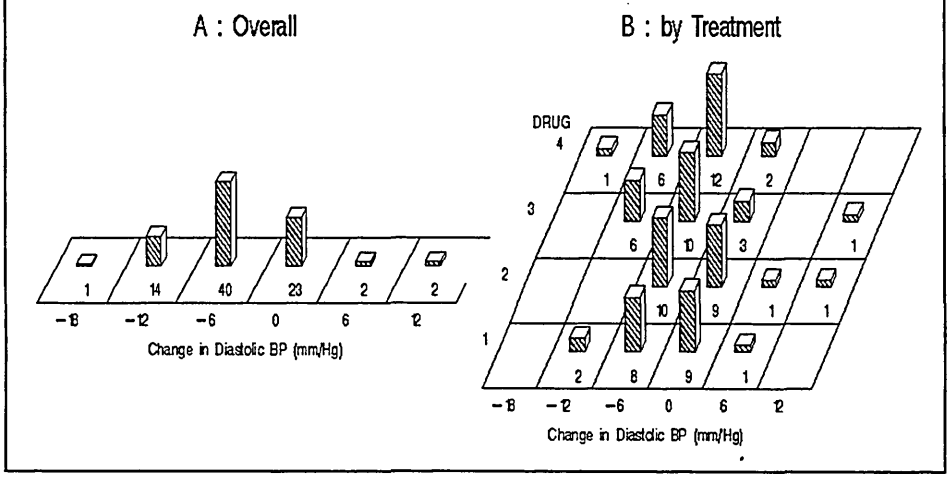


The findings for the change in the mean from baseline for method 1 (Figures 6.5.2A and B and Tables 8b-Appendix A) and for method 2 (Figures 6.6.2A and B and Tables 10b-Appendix A) agree with the results for the original data (Figures 5.1.2B and 5.2.2B and Table 5.1.2). Both figures for methods 1 and 2 were identical. Individuals on drugs 3 and 4 have larger changes than those individuals on drugs 1 and 2 ($p<0.001$ for both methods). Only drug 2 appears to be obviously skewed and the normal tests in Tables 8b (Appendix A) for method 1 and Table10b (Appendix A) for method 2 confirm this statement. It is believed that the individual on drug 2 with a change of between 15-25 mmHg is probably an outlier.

6.6.1.3 Diastolic BP (mmHg).

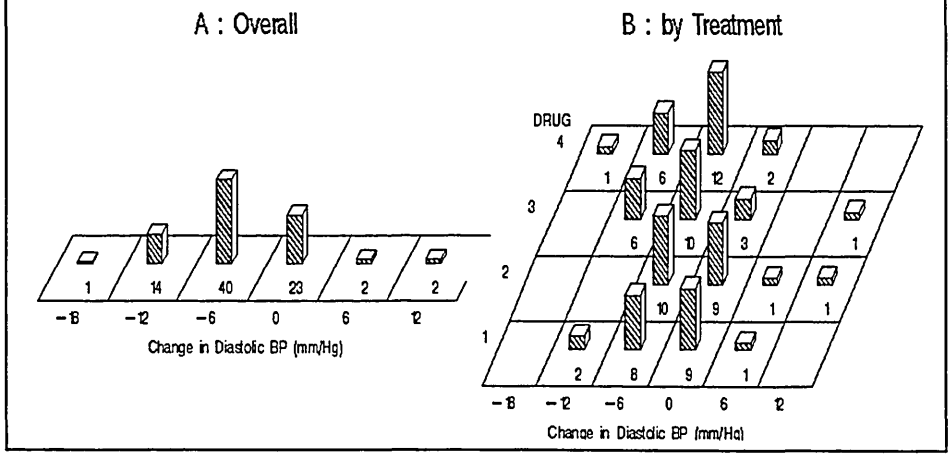
Method 1: Averaging Over Three Time Points

Figure 6.5.3
Block Charts of Change in Diastolic BP (mm/Hg) Values : Average of 3 Time Points



Method 2: Averaging Over Two Time Points

Figure 6.6.3
Block Charts of Change in Diastolic BP (mm/Hg) Values : Average of 2 Time Points

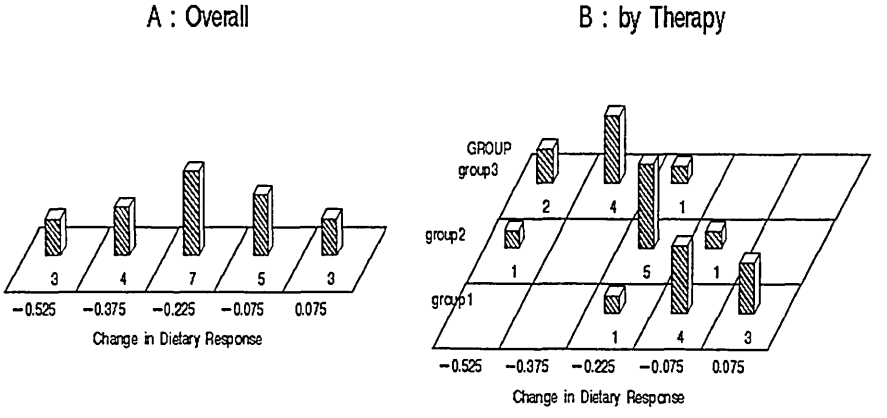


The findings for the change in the mean from baseline for method 1 (Figures 6.5.3A and B and Table 8c-Appendix A) and for method 2 (Figures 6.6.3A and B and Table 10c–Appendix A) agreed with those from the original data (Figures 5.1.3B and 5.2.3B and Table 5.1.3). Both figures for methods 1 and 2 were identical. The normal tests in Tables 8c and 10c (Appendix A) showed drugs 2 and 3 were not normally distributed. Figures 6.5.3B and 6.6.3B confirm this statement. For both methods 1 and 2, there was a treatment difference for the change in mean from baseline ($p<0.001$ for both methods). For both methods, there is a much larger average change in baseline for diastolic BP on drugs 3 and 4 (mean=-6.2 and -7.6 respectively) compared to drugs 1 and 2 (mean=-3.1 and –2.0 respectively).

6.6.1.4 Dietary Response

Method 1: Averaging Over Three Time Points

Figure 6.5.4
Block Charts of Change in Dietary Response Values : Average of 3 Time Point s



It can be seen that all change in mean from baseline data are normally distributed per therapy group using Tables 8d (Appendix A) and 5.1.4 for the data reduced using method 1 and for the original data respectively. This can also be seen in Figure 6.5.4B above for the reduced data using method 1 and also in Figures 5.2.4B for the original data. In both cases, the block-chart of the change in mean from baseline shows that there are obvious treatment differences ($p<0.001$). Group 1 has largest readings, group 2 has mid range readings and group 3 has the lowest readings.

6.6.2: Univariate Testing.

Six summary measures (mean, median, minimum, maximum, lower and upper quartiles) were calculated per treatment for each reduced data set both overall and by centre. Univariate normality and Kruskal-Wallis tests were conducted on the summary measures for the reduced data sets. Only results on the summary measures for the reduced data after data replacement are displayed since the findings on the reduced data both before and after data replacement gave similar conclusions. The findings for the summary measures on the reduced data after data replacement were compared with the findings for the summary measures on the original data before data replacement. Since the findings for the summary measures for the original data both before and after data replacement gave similar results [section 5.1], only findings for the original data before data replacement were used for comparison purposes.

6.6.2.1 Heart Rate (beats/min).

The summary measures were obtained for the data from both methods 1 (Table 8a – Appendix A) and 2 (Table 10a – Appendix A) respectively. The normal tests for all summary variables (mean, median, minimum, lower and upper quartile) apart from the maximum response agree for methods 1 and 2. The normal test for the maximum response for the original data before replacement shows that drug 2 is not normal, the maximum data from method 1 are all normally distributed per treatment group. Using method 2, the variable of maximum response for drug 4 is not normally distributed and all other drugs are normally distributed. This suggests that the data reduction may be reducing the effects of outliers in certain situations (namely with method 1) and increases the effects in other situations (method 2) and this in turn is influencing the results of the normal tests.

The Kruskal-Wallis tests for both method 1 (Table 8a –Appendix A) and method 2 (Table 10a – Appendix A) agree with one another. The results show no significant treatment differences per summary measure for both methods 1 ($p>0.667$) and 2 ($p>0.664$). These results also agreed with the findings for the original data before data replacement ($p>0.608$, Tables 5.1.1).

The summary measures from method 1 (Table 9a – Appendix A) and from method 2 (Table 11a – Appendix A) both after replacing missing data were tabulated by centre. Kruskal-Wallis tests were conducted on this data. It can be seen that all summary measures for both centres 1 and 2 showed no significant treatment differences as was the case with all prior analyses that were conducted on heart rate data.

6.6.2.2 Systolic Blood Pressure (mmHg)

The summary measures were obtained for the data from both methods 1 (Table 8b –Appendix A) and 2 (Table 10b –Appendix A) respectively. The normal test results for both methods 1 (Table 8b-Appendix A) and 2 (Table 10b – Appendix A) agreed with those findings for the original data before data replacement (Tables 5.1.2). All summary measures per treatment group are normally distributed.

The Kruskal-Wallis tests on the overall reduced segmentation data using methods 1 and 2 lead to similar conclusions as each other for all summary measures (mean, median, maximum, lower and upper quartile) apart from the minimum response. The minimum response for method 1 agrees with the results for the original data. Using method 1 there was significant evidence to suggest a treatment difference in the minimum response (p=0.020, Table 8b – Appendix A). For the original data before imputing missing records, there was significant evidence to suggest a treatment difference in the minimum response (p=0.022, Table 5.1.2). There was not significant evidence to suggest a treatment difference between the minimum response for reduced data using method 2 (p=0.052, Table 10b-Appendix A). Since the test result for method 2 was marginally significant, we will not worry about this any further.

Of all other Kruskal-Wallis tests conducted there was significant evidence to suggest a treatment difference for the mean, median, lower and upper quartile summary measures. There were no treatment differences detected for the maximum response for both methods 1 (p=0.079, Table 8b – Appendix A) and 2 (p=0.096, Table 10b – Appendix A). These findings agreed with those conclusions obtained for the original data (p=0.065, Table 5.1.2).

The summary measures from method 1 (Table 9b –Appendix A) and from method 2 (Table 11b – Appendix A) both after replacing missing data were tabulated by centre. Kruskal-Wallis tests were conducted on this data. It can be seen that all Kruskal-Wallis tests by centre conducted on the summary measures gave similar results for both methods 1 and 2. It was found that there were no significant treatment differences between any of the summary measures for centre 2 (p>0.065). For centre 1, treatment differences were detected for the mean (p=0.023 both methods 1 and 2), median (p=0.023 both methods 1 and 2), upper quartile (p=0.047 for method 1 and p=0.034 for method 2) and lower quartile (p=0.007 for method 1 and 0.012 for method 2). This by centre difference in results was also detected for the original data before replacement (Table 5.1.2). However, a difference in the maximum response for centre 1 was not detected for both reduction methods 1 (p=0.101) and 2 (p=0.064) but was detected for the original data (p=0.042).

6.6.2.3 Diastolic Blood Pressure (mmHg)

The summary measures on the reduced data using method 1 are displayed in Table 8c (Appendix A) and the results for method 2 are in Table 10c (Appendix A). Following normal tests on the summary measures it was found that all summary measures using method 2 (Table 10c – Appendix A) were normally distributed per treatment group. The results using method 1 (Table 8c –Appendix A) showed a skewed distribution for both the maximum and upper quartile on drug 1. The results on the original data (Table 5.1.3) showed that the maximum response on drug 1 was also non-normal. All other results were normal per treatment group and agreed for reduction using methods 1 and 2 and for the original data. The Kruskal-Wallis test results from method 1 (Table 8c-Appendix A) agree with those obtained for the original data before data replacement (Tables 5.1.3). There was significant evidence of a treatment difference for all variables ($p<0.022$) apart from the lower quartile ($p=0.069$) response. For method 2 (Table 10c –Appendix A), all summary measures apart from the minimum ($p=0.118$) response were significantly different between treatment groups ($p<0.037$).

The summary measures from method 1 (Table 9c –Appendix A) and from method 2 (Table 11c – Appendix A) both after replacing missing data were tabulated by centre. Kruskal-Wallis tests were conducted on this data. All Kruskal-Wallis tests conducted on the summary measures per centre gave similar results for data reduction methods 1 (Table 9c –Appendix A) and 2 (Table 11c –Appendix A) and both methods in turn agreed with the by centre results for the original data (Table 5.3.3). For centre 1, treatment differences were detected for the mean ($p=0.038$ both methods 1 and 2) and median ($p=0.017$ for method 1 and $p=0.026$ for method 2) responses. Other response treatment differences were observed for maximum ($p=0.009$ for method 1 and $p=0.004$ for method 2) and the upper quartile ($p=0.014$ for method 1 and $p=0.010$ for method 2). There were no treatment differences detected for any summary measures in centre 2.

6.6.2.4 Dietary Response.

Summary measures were obtained for dietary response data after data replacement reduced using method 1 only (Table 8d – Appendix A). The normal tests conducted on the data show that all summary measures per treatment group were normally distributed. These findings agree with the original data results (Table 5.1.4). The Kruskal-Wallis tests on the data reduced using method 1 (Table 8d-Appendix A) show treatment differences for all summary measures ($p<0.001$ in all cases). This again agrees with the findings for the original data (Table 5.1.4).

6.7 Overview

Only the multivariate principal components analysis (P.C.A.) approach of data reduction stated in the chapter above was affected by the missing nature of the data. SAS was used to analyse the data set. It was decided to analyse the data using both univariate and multivariate parametric techniques. The univariate methods conducted in the chapter above were applied to only the data retaining an element of time. It was found that the univariate results both before and after data replacement gave similar findings. Comparisons were made between the univariate results on the reduced data after data replacement and the original data before data replacement. It was found that in all cases, the results using data reduction method 1 were consistent with those on the original data for the overall data. There were slight discrepancies in the findings for method 2 compared with the original data for systolic and diastolic blood pressure but they were not of concern.

Multivariate tests were applied to the data following all methods of data reduction described in the chapter above and on the original data both before and after imputing missing data. All results were then compared. An optimal approach of reducing the data was then suggested based on all multivariate test results. All multivariate tests and corresponding results are described in chapter 7 below.

CHAPTER 7: Multivariate Testing

7.0 Introduction

Multivariate methods were applied to the data following all methods of data reduction described in chapter 6 and on the original data both before and after imputing missing data. All results were then compared. Any multivariate testing performed on the data and results obtained are explained in the following chapter. The multivariate test used to test between treatment groups was based on the Mahalanobis D^2 statistic.

An optimal approach of reducing the data was suggested based on the multivariate test results. The optimal approach was one where normality tests would not be required and the assumption of asymptotic normality could be applied to the data. This in turn would lead to valid robust multivariate testing procedures.

7.1 Methods

Following the three methods of data reduction (summary measures, P.C.A. and segmentation of the data) mentioned in chapter 6, we were left with four reduced data sets for data sets A and three reduced data sets for data set B both before and after imputing missing records. The Mahallanobis Distances, from a discriminant analysis viewpoint, were used to test for paired group difference in distance for each of the data sets that were available. The data sets were as follows:

a) Data sets A and B both before and after imputing missing data.

b) Principal Components Analysis (P.C.A.) vector, on data sets A and B, both before and after imputing missing records. A principal component analysis was conducted on the data and the first 10 principal components were selected to represent the data both before and after data replacement for the vital signs data and the first 5 principal components were selected to represent the dietary response data.

c) Grouped mean vector of average of observations at 3 successive time points (method 1) for data sets A and B, both before and after imputing missing records. Grouped mean vector of average of 2 times (method 2) for data set A only, both before and after imputing missing records.

d) Summary Measures (S.M.) vector, for data sets A and B, both before and after imputing missing records. Six summary measures (mean, median, minimum maximum, lower and upper quartile) were each calculated both before and after data replacement. They were calculated for the original data and also for the data using methods 1 and 2 for data reduction. All six summary measures were analysed together in a multivariate manner.

Any similarities or differences between the results from the various approaches were noted and discussed whenever appropriate.

The original data of 24 or 9 readings, the 8 or 3 readings using method 1, the 12 readings using method 2, the 10 or 5 readings using the P.C.A and each of the S.M. vector of 6 readings were each analysed as a multivariate vector. This was the case both before and after replacement of missing data. All results are displayed in Table 7.1.1 to 7.1.4 below.

7.2 Results

7.2.1: Heart Rate (beats/min)

Table 7.1.1
Mahalanobis Distances and p-values for Each Multivariate Vector: Heart Rate (b/m).

Data Format		Treatment Distances					
		1→2	1→ 3	1→4	2→3	2→ 4	3→4
Original Data (N=73)	Distance^2	4.73	3.92	2.21	3.74	5.11	2.33
Before Data Replaced	P-value	*0.319*	*0.574*	*0.950*	*0.501*	*0.171*	*0.911*
S. Measures (N=86)	Distance^2	0.475	0.299	0.297	0.760	0.916	0.261
Before Data Replaced	P-value	*0.574*	*0.804*	*0.816*	*0.264*	*0.177*	*0.851*
Original Data (N=84)	Distance^2	3.51	2.21	1.95	3.32	4.73	2.07
After Data Replaced	P-value	*0.355*	*0.856*	*0.909*	*0.445*	*0.104*	*0.892*
S. Measures (N=84)	Distance^2	0.485	0.373	0.271	0.767	0.923	0.235
After Data Replaced	P-value	*0.563*	*0.731*	*0.847*	*0.289*	*0.174*	*0.892*
Prin. Comps. (N=73)	Distance^2	0.016	0.014	0.041	0.018	0.046	0.056
Before Data Replaced	P-value	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
Prin. Comps. (N=84)	Distance^2	0.019	0.036	0.016	0.024	0.016	0.056
After Data Replaced	P-value	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
3HR Av. Grp (N=74)	Distance^2	0.863	1.060	0.685	1.264	1.544	1.039
Before Data Replaced	P-value	*0.402*	*0.290*	*0.588*	*0.168*	*0.074*	*0.303*
S.Measure. (N=86)	Distance^2	0.724	0.365	0.327	0.761	0.667	0.151
3HR Av. Grp Before	P-value	*0.307*	*0.719*	*0.778*	*0.263*	*0.358*	*0.956*
3HR Av. Grp (N=84)	Distance^2	0.864	1.039	0.657	1.269	1.522	0.953
After Data Replaced	P-value	*0.402*	*0.303*	*0.616*	*0.167*	*0.079*	*0.364*
S.Measure. (N=84)	Distance^2	0.721	0.252	0.353	0.657	0.720	0.198
3HR Av. Grp After	P-value	*0.310*	*0.875*	*0.746*	*0.384*	*0.311*	*0.926*
2HR Av. Grp (N=83)	Distance^2	1.056	1.454	0.748	1.751	1.634	1.074
Before Data Replaced	P-value	*0.635*	*0.424*	*0.864*	*0.250*	*0.263*	*0.680*
S.Measure. (N=86)	Distance^2	0.336	0.639	0.199	0.450	0.270	0.368
2HR Av. Grp Before	P-value	*0.757*	*0.385*	*0.921*	*0.592*	*0.840*	*0.715*
2HR Av. Grp (N=84)	Distance^2	1.078	1.408	0.730	1.779	1.677	1.082
After Data Replaced	P-value	*0.617*	*0.427*	*0.873*	*0.217*	*0.242*	*0.652*
S.Measure. (N=84)	Distance^2	0.330	0.666	0.208	0.400	0.298	0.348
2HR Av. Grp After	P-value	*0.766*	*0.391*	*0.913*	*0.686*	*0.806*	*0.763*

* Significant results

All results are displayed in Table 7.1.1 and it can be seen that in all cases there are no significant treatment differences for heart rate data. These results all agree with all methods conducted thus far.

7.2.2: Systolic Blood Pressure (mmHg)

Table 7.1.2
Mahalanobis Distances and p-values for Each Multivariate Vector: SBP (mmHg)

Data Format		Treatment Distances					
		1→2	1→3	1→4	2→3	2→4	3→4
Original Data (N=84)	Distance^2	3.95	5.19	6.34	4.46	3.47	3.29
Before Data Replaced	P-value	*0.514*	*0.275*	*0.107*	*0.313*	*0.556*	*0.666*
S. Measures (N=86)	Distance^2	0.576	0.254	1.266	0.633	0.767	0.976
Before Data Replaced	P-value	*0.453*	*0.858*	*0.065*	*0.376*	*0.272*	*0.147*
Original Data (N=73)	Distance^2	2.69	2.99	4.21	3.82	1.86	2.71
After Data Replaced	P-value	*0.652*	*0.591*	*0.200*	*0.291*	*0.920*	*0.692*
S. Measures (N=84)	Distance^2	0.555	0.321	1.353	0.541	0.767	0.930
After Data Replaced	P-value	*0.478*	*0.796*	**0.050***	*0.510*	*0.273*	*0.194*
Prin. Comps. (N=73)	Distance^2	0.029	0.104	1.208	0.035	0.939	0.649
Before Data Replaced	P-value	*1.000*	*1.000*	*0.528*	*1.000*	*0.633*	*0.869*
Prin. Comps. (N=84)	Distance^2	0.088	0.124	1.144	0.009	0.623	0.539
After Data Replaced	P-value	*1.000*	*1.000*	*0.399*	*1.000*	*0.813*	*0.891*
3HR Av. Grp (N=74)	Distance^2	0.762	1.100	1.795	0.755	0.845	0.867
Before Data Replaced	P-value	*0.495*	*0.265*	**0.042***	*0.520*	*0.418*	*0.434*
S.M. 3HR Av. Grp	Distance^2	0.803	0.411	1.519	0.355	0.878	0.927
Before (N=86)	P-value	*0.246*	*0.657*	**0.029***	*0.720*	*0.197*	*0.171*
3HR Av. Grp (N=84)	Distance^2	0.745	1.127	1.791	0.776	0.838	0.885
After Data Replaced	P-value	*0.511*	*0.249*	**0.042***	*0.500*	*0.424*	*0.419*
S.M. 3HR Av.Grp	Distance^2	0.768	0.372	1.534	0.260	0.861	0.793
After (N=84)	P-value	*0.273*	*0.733*	**0.028***	*0.860*	*0.209*	*0.282*
2HR Av. Grp (N=83)	Distance^2	1.347	1.722	2.239	1.699	1.375	1.056
Before Data Replaced	P-value	*0.424*	*0.280*	*0.089*	*0.274*	*0.407*	*0.693*
S.M. 2HR Av.Grp	Distance^2	0.767	0.583	2.040	0.106	0.721	0.778
Before (N=86)	P-value	*0.272*	*0.445*	**0.006***	*0.981*	*0.309*	*0.264*
2HR Av. Grp (N=84)	Distance^2	1.314	1.703	2.229	1.692	1.367	0.980
After Data Replaced	P-value	*0.445*	*0.266*	*0.090*	*0.254*	*0.411*	*0.726*
S.M. 2HR Av.Grp	Distance^2	0.806	0.740	1.961	0.204	0.706	0.857
After (N=84)	P-value	*0.245*	*0.324*	**0.007***	*0.917*	*0.323*	*0.237*

* Significant results

It can be seen that significant differences were detected between drug 1 and 4 only. Differences were detected using method 1 both before and after data replacement (p=0.042 in both cases) and for the corresponding matrix of summary measures (p=0.029 before replaced and p=0.028 after replaced). The actual data using the grouped average method 2 did not show up any significant treatment differences. However, the summary measures on the data using method 2 both before (p=0.006) and after (p=0.007) data replacement showed a significant treatment difference between drugs 1 and 4. None

of the other methods showed any significant treatment differences. After looking more closely at the table it can be seen that the summary measures on the data both before (p=0.065) and after data replacement (p=0.05) are marginally significant. This is also the case with the original data from method 2 both before (p=0.089) and after (p=0.09) data replacement. There were no differences detected using the principal component analysis or for the original data both before and after data replacement (p>0.107).

7.2.3: Diastolic Blood Pressure (mmHg)

Table 7.1.3
Mahalanobis Distances and p-values for Each Multivariate Vector: DBP (mmHg)

Data Format		Treatment Distances					
		1→2	1→ 3	1→4	2→3	2→ 4	3→4
Original Data (N=73)	Distance^2	2.44	6.95	4.73	6.97	3.89	4.23
Before Data Replaced	P-value	*0.909*	*0.076*	*0.342*	**0.038***	*0.429*	*0.395*
S. Measures Before Data	Distance^2	0.78	1.28	1.15	1.45	2.01	1.33
Replaced (N=86)	P-value	*0.260*	*0.056*	*0.092*	**0.029***	**0.005***	**0.049***
Original Data (N=84)	Distance^2	1.55	5.47	3.87	5.90	3.38	3.50
After Data Replaced	P-value	*0.970*	*0.059*	*0.276*	**0.031***	*0.396*	*0.410*
S. Measures After Data	Distance^2	0.64	1.08	1.28	1.46	1.97	1.41
Replaced (N=84)	P-value	*0.382*	*0.125*	*0.063*	**0.037***	**0.006***	**0.047***
Prin. Comps. (N=73)	Distance^2	0.003	0.283	0.789	0.268	0.765	0.139
Before Data Replaced	P-value	*1.000*	*0.995*	*0.811*	*0.993*	*0.767*	*1.000*
Principal Components	Distance^2	0.010	0.397	0.759	0.382	0.734	0.063
After Data Replaced	P-value	*1.000*	*0.959*	*0.715*	*0.962*	*0.722*	*1.000*
3HR Grp Av Before Data	Distance^2	0.352	1.556	1.377	1.162	1.049	0.820
Replaced (N=73)	P-value	*0.898*	*0.087*	*0.126*	*0.2162*	*0.264*	*0.475*
S.M. 3 Hr Grp Av	Distance^2	0.622	0.870	1.242	1.829	1.697	1.497
Before (N=86)	P-value	*0.403*	*0.202*	*0.070*	**0.008***	**0.015***	**0.028***
3HR Grp Av After Data	Distance^2	0.352	1.561	1.364	1.164	1.034	0.852
Replaced (N=84)	P-value	*0.898*	*0.086*	*0.130*	*0.215*	*0.274*	*0.447*
S.M. 3 Hr Grp Av	Distance^2	0.580	0.506	1.278	1.403	1.673	1.260
After (N=84)	P-value	*0.449*	*0.566*	*0.063*	**0.043***	**0.016***	*0.074*
2HR Grp Av Before Data	Distance^2	0.656	2.363	1.414	2.611	1.827	1.249
Replaced (N=83)	P-value	*0.904*	*0.088*	*0.403*	**0.048***	*0.184*	*0.557*
S.M. 2 Hr Grp Av	Distance^2	0.565	0.383	0.864	0.933	1.190	0.363
Before (N=86)	P-value	*0.465*	*0.694*	*0.218*	*0.157*	*0.076*	*0.721*
2HR Grp Av After Data	Distance^2	0.653	2.540	1.406	2.833	1.842	1.317
Replaced (N=84)	P-value	*0.905*	*0.054*	*0.406*	**0.025***	*0.177*	*0.486*
S.M. 2 Hr Grp Av	Distance^2	0.534	0.434	0.865	0.988	1.223	0.448
After (N=84)	P-value	*0.502*	*0.655*	*0.218*	*0.154*	*0.069*	*0.638*

* Significant results

It can be seen that significant differences were detected between drug 2, 3 and 4 only. Differences were detected mainly between drugs 2 and 3 both before and after data replacement for the original data (p=0.038 and 0.031 respectively) and on the corresponding summary measures (p=0.029 and 0.037) respectively. Also for the data both before and after data replacement for summary measures on the reduced data using method 1 (p=0.008 and 0.043 respectively) and on the actual reduced data using method 2 (p=0.048 and 0.025). The differences between drugs 2 and 4 were only detected both before and after data replacement for the summary measures on the original data (p=0.005 and 0.006 respectively) and on the grouped data using method 1 (p=0.015 and 0.016). A treatment difference was found between drugs 3 and 4 for both the data before and after replacement using the summary measures on the original data (p=0.049 and 0.047 respectively) and only for the data before replacement for the reduced data using method 1 (p=0.028). The summary measures approach tended to allow detection of treatment differences. There were no differences detected using the principal component analysis.

7.2.4: Dietary Response

Table 7.1.4:
Mahalanobis Distances and p-values for Each Multivariate Vector: Dietary Data

Vector		Treatment Distances		
		1→2	1→ 3	2→3
Original Data (N=20)	Distance^2	21.1	171.9	82.0
Before Data Replaced	P-value	**0.020***	**<0.001***	**<0.001***
S. Measures Before Data	Distance^2	8.5	31.7	16.7
Replaced (N=24)	P-value	**0.009***	**<0.001***	**<0.001***
Original Data (N=22)	Distance^2	16.8	165.4	85.3
After Data Replaced	P-value	**0.017***	**<0.001***	**<0.001***
S. Measures After Data	Distance^2	7.4	31.8	14.3
Replaced (N=22)	P-value	**0.029***	**<0.001***	**0.003***
Prin. Comps. (N=22)	Distance^2	9.919	38.37	9.285
Before Data Replaced	P-value	**0.007***	**<0.001***	**0.012***
Prin. Comps. After Data	Distance^2	8.0	33.1	8.6
Replaced (N=22)	P-value	**0.009***	**<0.001***	**0.009***
3HR Av Grp (N=24)	Distance^2	8.4	94.6	53.3
Before Data Replaced	P-value	**<0.001***	**<0.001***	**<0.001***
S.Measure. (N=24)	Distance^2	7.4	22.8	9.4
3HR Av Grp Before	P-value	**0.016***	**<0.001***	**0.006***
3HR Av Grp (N=22)	Distance^2	9.8	100.7	53.2
After Data Replaced	P-value	**<0.001***	**<0.001***	**<0.001***
S.Measure. (N=22)	Distance^2	8.4	27.5	7.9
3HR Av Grp After	P-value	**0.018***	**<0.001***	**0.028***

* Significant results

Table 7.1.4 showed a significant difference in every pair of therapy groups that were tested. These results were consistent with all other methods conducted thus far.

7.3 Overview

The findings for tests before and after data reduction are similar in nature. However, in the latter case, the tests turn out to be more robust and hence the corresponding results tend to be more reliable. In the case of non-normal data, the test findings relative to the original data can not be viewed as very reliable. This is especially so because the sample size of 24 for a treatment group can not be considered to be large enough in the case when there are p=24 time points. The results given in the present chapter are based on Mahalanobis D^2. This test statistic assumes that all treatment groups have the same variance-covariance matrix. One could relax the assumptions concerning the variance-covariance matrices using a likelihood ratio test; essentially Wilks theorem asserts that when p time points is moderate and the sample sizes are large, the test is equivalent to a χ^2 test. Although this latter test could also be considered to be robust in the case of reduced data, it is not dealt with in this thesis.

Among various methods of data reduction that are addressed in this chapter, only the approach of averaging the observations at three successive time points (method 1) seems to retain the information on the performances of treatments at various time points. This is especially so, if it is assumed that there is not much variation between observations at two successive time points (method 2).

All modelling methods applied to the continuous and categorical data and corresponding results are described in the following chapter 8.

CHAPTER 8: Parametric and Non-Parametric Modelling

8.0 Introduction

Both the continuous and categorical data were modelled using various modelling approaches.

Categorical data set A following classification by vital sign status (Listing 3.3) and the summary measures of these categorical data (Listing 3.5) were modelled using the following methods:

A time to event (where the event was the first abnormally 'high' reading) survival analysis approach [section 8.1.1] was conducted. Also, the number of individuals with either at least 50% or 75% of abnormally 'high' readings over the course of the study was modelled using a logistic regression approach [section 8.1.2]. This second approach was not applied to the heart rate data since there were no individuals with more than 50% of abnormally 'high' heart rate readings.

The reduction in continuous data from 24 time points to either 8 or 12 time points for data set A (vital signs) and from 9 to 3 on-treatment time points for data set B (dietary response) was required for the assumption of asymptotic normality or robustness of tests to hold. The assumption in question was one of the most important conditions required to conduct any multivariate analysis methods on the data.

Once it was determined how the data was behaving following the plotting and multivariate testing (using Mahalanobis D^2) of the data, the original data was described using a multivariate model [8.2] on the reduced data. A mixed modelling approach [8.2.1] was used to model the continuous data sets (Listings 3.1.1 and 3.2.1 for the original data sets A and B, Listings 6.1 and 6.3 for reduced data set A using methods 1 and 2 and Listing 6.2 for reduced data set B using method 1).

The original data before data replacement and the reduced time data after data replacement (using both methods 1 and 2 for vital signs data and method 1 only for dietary response data) were all finally modelled using a generalised mixed effects model. In all cases, the final model had random subject effects and adjustments for baseline readings. All other effects in the model were fixed. The final model based mean and 95% CI was plotted for each data structure that was analysed.

Finally, an optimal method of multivariate analysis of the data was devised.

8.1 Categorical Data Analysis

8.1.1: Survival Analysis on the Time to an Abnormal Result.

In this case, the variable 'HIGH' was used. Any missing data was set to '0' (having 'no' 'high' result) and the data set was viewed in a univariate format. The occurrence of a 'high' result was considered to be an event= "yes". The time to the event was the time of the first 'high' reading. If an individual never had a 'high' reading, then they were censored with and event= "no" and time to event of 24 hours. A Kaplan-Meier survival analysis approach [section 2.2.5] was conducted for the time to the first abnormally 'high' reading and the corresponding results are displayed in Tables 19a to 19c (Appendix A). Wilcoxon and Log-rank tests are also displayed in these tables. The survival rates are displayed visually in Figures 8.1.1-8.1.4 below. In conclusion, there were no treatment differences for the time to an abnormal result for any of the vital sign measurements.

8.1.1.1 Heart Rate (beats/min)

Figure 8.1.1:
Kaplan-Meier Cumulative Survival Plot For Time to First Abnormal Heart Rate Over 24 hours.

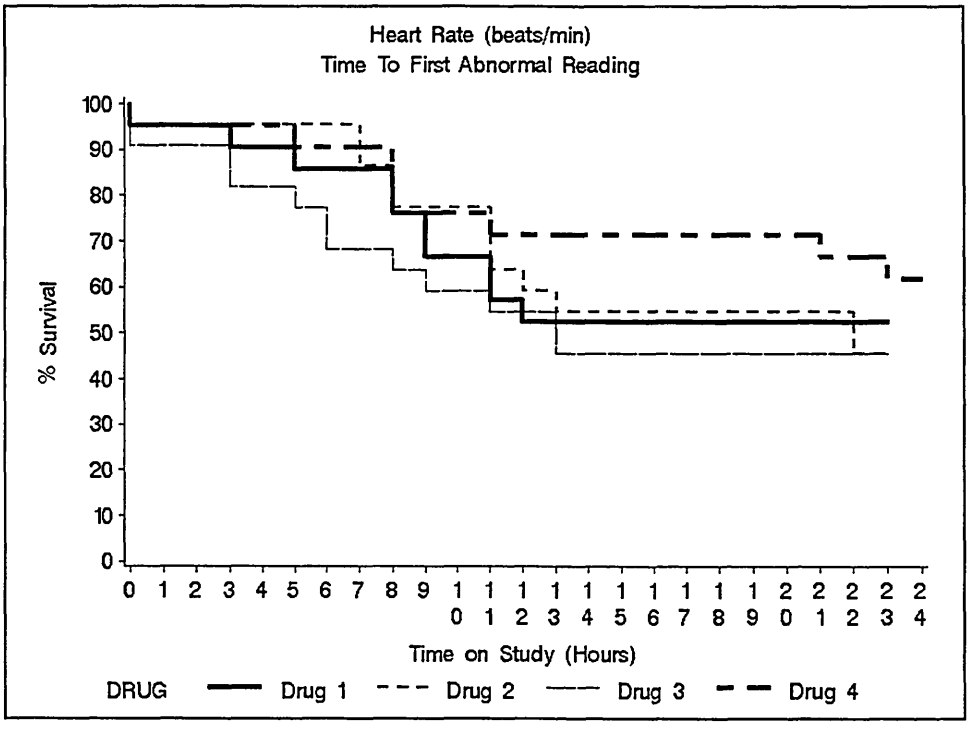


Figure 8.1.1 above shows the cumulative survival plot over time. Table 19a (Appendix A) shows the cumulative survival rates for the time to incidence data. From this table, it can be seen that most individuals on drugs 2 and 3 had an event by time 24 since 54.6% failed in both cases. Only 38.1% individuals on drug 4 failed by time 24 hours. Those individuals on drug 2 did not have an event until time 7 hours and individuals on drug 4 did not have the first event until time 5 hours. The other two

drugs 1 and 3 initially failed at time 3 hours. Following the Log-rank test (p=0.590) it can be seen that there were no treatment differences in time to occurrence of the first abnormal event.

8.1.1.2: Systolic Blood Pressure

Figure 8.1.2:
Kaplan Meier Cumulative Survival Plot For Time to First Abnormal Systolic BP Over 24 Hrs.

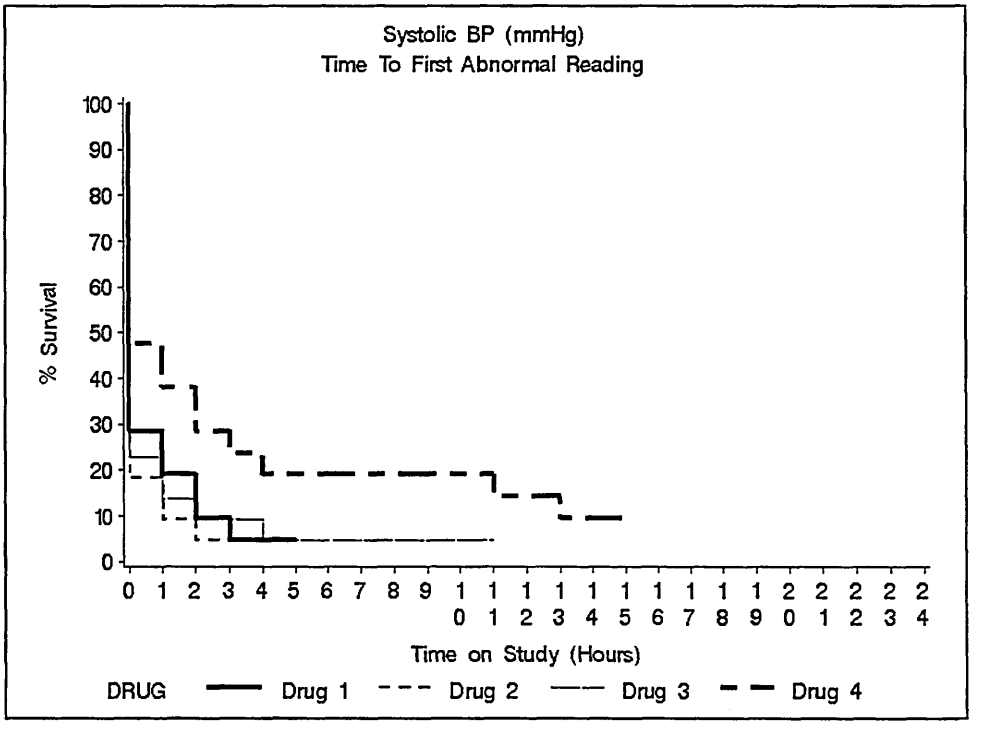


Figure 8.1.2 shows the cumulative survival plot over time. Table 19b (Appendix A) shows the cumulative survival rates for the time to incidence data. From this table, it can be seen that most individuals on drug 2 had an event by time 3 (95.5 % failed). For drug 1, there were 95.3% of individuals that failed at time 5 hours. For drug 3, 95.5% of individuals failed at time 11 hours and for drug 4, 81% of individuals failed at time 11 hours. At time 24 all individuals remaining without an event were censored. There was greater than 95% failure for drugs 1 to 3 overall. Individuals on drug 4 had a 90.5% failure rate at this final time point. Following the Log-rank test, it can be seen that there were no treatment differences in time to occurrence of the first abnormal event (p=0.263).

8.1.1.3: Diastolic Blood Pressure

Figure 8.1.3:
Kaplan Meier Cumulative Survival Plot For Time to First Abnormal Diastolic BP Over 24 Hrs.

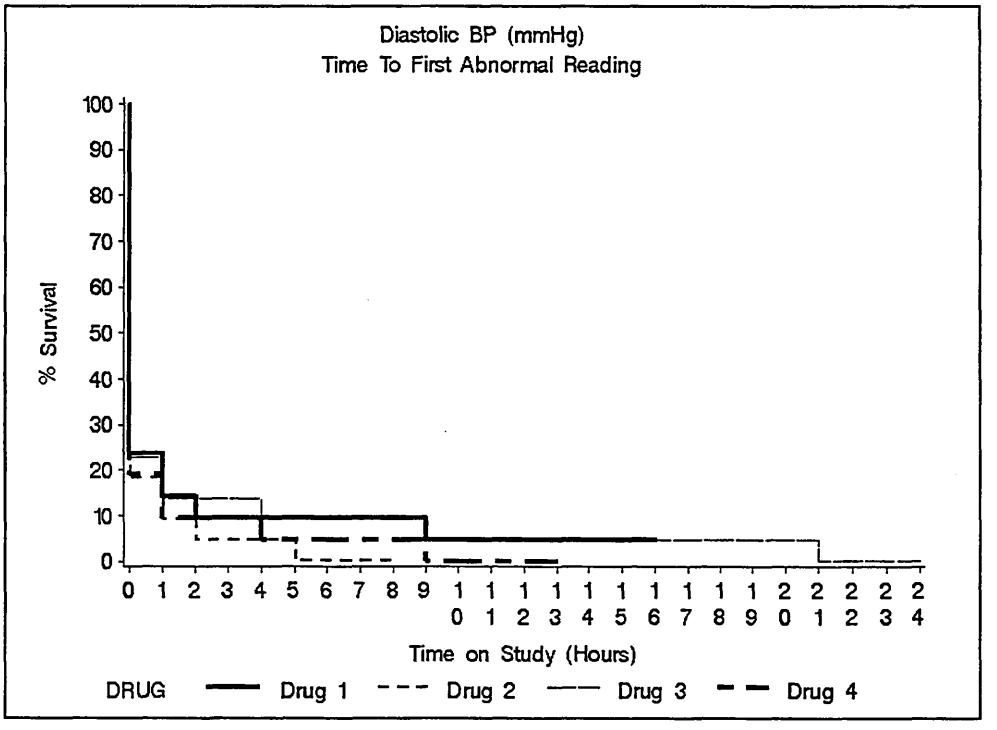


Figure 8.1.3 shows the cumulative survival plot over time. Table 19c (Appendix A) shows the cumulative survival rates for the time to incidence data. From this table, it can be seen that all individuals on drug 2 had a high result by time 8 hours (100 % failed). For drug 4, 100% failed by time 13 hours and for drug 3 100% failed or had at least one abnormal result by time 24 hours. Only drug 1 had one individual that survived past the end of the study without having even one high reading. The Log-rank test (p=0.412) shows that there were no treatment differences in time to occurrence of the first abnormal event for diastolic blood pressure.

8.1.2: Logistic Regression on having greater than 50% or greater than 75% of Abnormally "High" Results.

There was only a maximum of 6 abnormally high heart rate readings for any patient, so this type of testing for heart rate data was considered to be of no use. The following tests were conducted for systolic and diastolic blood pressure readings only. A logistic regression analysis [section 2.2.7] was conducted on frequency of having greater than 50% abnormality or greater than 75% abnormality for both variables mentioned. A dummy variable was created for each drug (1 to 3) vs. drug 4. The three dummy variables for drug together with interactions between each main effect and a centre dummy variable were modelled. The initial test was conducted by modelling the interaction between centre and drug and if a significant interaction effect was not found, then only the main effects were tested in a reduced model. Tables 17b and 18b (Appendix A) show respective estimates and results obtained for having greater than 50% and 75% abnormality for systolic blood pressure. Tables 17c and 18c (Appendix A) show the respective estimates and the results obtained for having greater than 50% and 75% abnormality for diastolic blood pressure.

8.1.2.1 Systolic Blood Pressure

A) Greater than 50% Abnormality.

The outcome of having a frequency of 50% or more abnormality was modelled after adjusting for centre (Table 17b-Appendix A).

Full Model:

For the full model, none of the interactions in the model were significant ($p<0.187$). Hence all interactions were removed and only the reduced model was fitted.

Final: Reduced Model:

In this case there was significant evidence of an effect for drug 1 compared with drug 4 ($p=0.032$). All other treatment effects (for drugs 2 and 3 compared to drug 4) were marginally significant ($p=0.051$ in both cases). In all cases, there was an odds ratio of greater than 3.5 in favour of the other drug over drug 4. This treatment difference was not picked up with the Chi-squared test ($p=0.075$) in Table 16b (Appendix A).

B) Greater than 75% Abnormality.

The outcome of the frequency of 75% or more abnormality was modelled after adjusting for centre (Table 18b –Appendix A).

Full Model:

For the full model, none of the interactions in the model were significant ($p<0.613$). Hence all interactions were removed and only the reduced model was fitted.

Final: Reduced Model:

In this case there was significant evidence of an effect for drug 1 compared with drug 4 ($p=0.007$) and drug 2 compared to drug 4 ($p=0.029$). The effect of drug 3 compared to drug 4 was insignificant ($p=0.088$) in the model. The odds ratio was 10.5 times in favour of drug 1 over drug 4 and 6.6 times in favour of drug 2 over drug 4. The treatment differences were also picked up with the Chi-squared test result ($p=0.025$) in Table 16b (Appendix A).

C) Overall Conclusion:

For systolic blood pressure, the final logistic regression models for the proportion of individuals with greater than or equal to 50% abnormality and 75% abnormality gave similar findings, showing that there was a significant effect for drug 1 compared to drug 4 ($p<0.032$). For the proportion of individuals with greater than or equal to 75% abnormality, there was also a significant treatment difference between drugs 2 and 4 ($p=0.029$). This finding was also marginally obvious using the proportion of individuals with greater than or equal to 50% abnormality ($p=0.051$). The Chi-squared tests conducted in Table 16b (Appendix A) confirm the findings for the models on the proportion of individuals with greater than or equal to 75% abnormality only, suggesting that there is indeed a treatment difference between drugs 2 and 4 and also 1 and 4.

8.1.2.2 Diastolic Blood Pressure

A) Greater than 50% Abnormality.

The outcome of the frequency of 50% or more abnormality was modelled after adjusting for centre (Table 17c-Appendix A).

Full Model:

For the full model, none of the interactions in the model were significant ($p<0.112$). Hence all interactions were removed and only the reduced model was fitted.

Final: Reduced Model:

In this case there was significant evidence of an effect for drug 1 compared with drug 4 ($p=0.047$). All other treatment effects (for drugs 2 and 3 compared with drug 4) were not significantly different. The odds ratio of greater than 4.6 in favour of the other drug over drug 4. This treatment difference was not detected with the Chi-squared test result ($p=0.062$) in Table 16c (Appendix A).

B) Greater than 75% Abnormality.

The outcome of the frequency of 75% or more abnormality was modelled after adjusting for centre (Table 18c –Appendix A).

Full Model:

For the full model, none of the interactions in the model were significant ($p<0.346$). Hence all interactions were removed and only the reduced model was fitted.

Final: Reduced Model:

In this case there was no evidence of any significant treatment effect ($p>0.524$). This result agrees with the Chi-squared tests that were conducted in Table 16c (Appendix A).

C) Overall Conclusion:

For diastolic blood pressure, proportion of individuals with greater than 50% abnormality, there was significant evidence of a treatment effect for drug 1 compared with drug 4 ($p=0.047$). This difference was not detected, however, for the proportion of individuals with greater than 75% abnormality. The Chi-squared tests conducted in Table 16c (Appendix A) confirm the findings for the models on the proportion of individuals with greater than or equal to 75% abnormality only, suggesting no treatment differences.

8.2 Continuous Data Analysis

It was believed that data reduction methods are the best way to get valid multivariate test results and the aim here is to see whether the methods do indeed give valid comparable results for the final models selected to describe the data.

Modelling the original data (assuming normality) gave an idea of the pattern for the actual observed mean response over time. The reduced data (where normality did not need to be tested) was modelled since the assumption of multivariate normality was based on an asymptotic theory requiring the number of individuals to be large and the number of observations for an individual to be small. Some researchers have claimed that multivariate analysis of variance can not be applied if this scenario is not met since there can be convergence problems. This is especially true when using Proc GLM in SAS.

The model on the original data was studied in conjunction with the models for the reduced data using methods 1 and 2 respectively. The original data was only modelled for comparison purposes.

The data could have been modelled using Proc GLM. The problem was that Proc GLM could not handle either missing data or unbalanced data structures when it came to multivariate analysis. Hence, it was decided to use Proc MIXED with the 'REPEATED' statement since it catered for most of the shortcomings of Proc GLM. Using this approach, there was no issue with missing or unbalanced data and the original data could also be modelled without any convergence problems since the variance-covariance matrix could be selected before running the model. SAS iterated the covariance parameter estimated using the REML approach.

A modified version of the mixed effects model [section 2.4.3 – (e), page 39] with additional components for time and centre (when available) was selected to model the data [section 8.2.1].

For the original data, only the mixed effects model with a compound symmetry variance-covariance structure would converge, due to the large number of repeated measurements. The preferred unstructured variance-covariance matrix for repeated measures data could, however, be selected for the reduced data.

8.2.1: Mixed Modelling

Proc MIXED was used to model the mean response data using a multivariate generalised mixed modelling approach. Following essentially the modelling methods of Crowder and Hand[14] the original model (combining both the random effect and error terms) for data set A can be expressed follows:

$$y_{ijkl} = \mu + \alpha_i + \beta_k + \delta_l + \gamma_{ik} + \varepsilon_{ijkl} \quad [6]$$

Here μ would be the grand mean adjusting for baseline measurement, α_i would represent fixed group effects, β_k would represent the fixed time effects, δ_l would represent the fixed centre effects, γ_{ik} would be the group by time interaction effects and ε_{ijkl} are random. We assume in the model the vectors (ε_{ij1l}..... ε_{ijpl}) to be mutually independent and identically distributed with zero mean vector, for distinct ijl.

The original model selected for data set B and the final model for both data sets A and B is as follows:

$$y_{ijk} = \mu + \alpha_i + \beta_k + \gamma_{ik} + \varepsilon_{ijk} \quad [7]$$

Here μ would be the grand mean adjusting for baseline measurement, α_i would represent fixed group effects, β_k would represent the fixed time effects, γ_{ik} would be the group by time interaction effects and ε_{ijk} are random. We assume in the model the vectors (ε_{ij1} ..... ε_{ijp}) to be mutually independent and identically distributed with zero mean vector, for distinct ij.

Note that the models [6] and [7] above can also be interpreted as means models.

For each of the vital sign variables, the original data both before and after imputing missing records and the reduced imputed data by averaging across either two or three time points were modelled. For the dietary data, the original data both before and after imputing missing records and the imputed data averaged across three time points were modelled.

Initially, the original data were modelled both before and after imputing missing records. The results for both approaches were similar and therefore only the results on the original data before imputing missing data were considered for comparison purposes.

Only the reduced data following the regeneration of data was modelled for reasons of consistency with any previous analyses conducted for this study. The data sets using the average of two or three times for data set A and the average of three times for data set B were modelled independently.

A mixed modelling approach was taken to analyse the mean response profile for both the original and reduced data sets. The data was modelled as a combination of both fixed and random effects. Individuals were treated as (contributing to) random effects and all other effects were fixed. Interactions between time and drug were modelled with adjustments being made for 'time' and 'baseline readings' for both data sets A and B and an addition adjustment was made for 'centre' for data set A. This was considered to be the full model.

Note: [6] shows the full model structure for data set A and [7] shows the full model structure for data set B. The models for the original data sets were fitted using a compound symmetry (CS) variance-covariance matrix and for the reduced data sets were fitted using an unstructured (UN) variance-covariance matrix.

Various models after removing insignificant effects and interactions were also looked at. All p-values from the various mixed models that were applied to model the vital signs and dietary response data over the course of study are displayed in Tables 8.1.1 to 8.1.4 for heart rate, systolic blood pressure, diastolic blood pressure and dietary response respectively.

For all vital sign measurements, the 'centre' effect and 'interaction' term were both insignificant effects in the model. After comparing results it was found that the results before and after adjusting for 'centre' for data set A were very similar. Hence, it was decided to remove the insignificant 'centre' term (since this gave no additional information) but to keep the insignificant 'interaction' term in all the final models to best describe the data over time for all vital sign measurements.

Note: [7] shows the final model for both data sets A and B.

The SAS output for the final models of both the original and reduced data are displayed in Tables 20a to 20d (Appendix A).

A least squares approach was used to estimate the means and 95% CI for the final model after adjusting for 'baseline reading' and 'time' effects only. The models were conducted for the original vital signs data before replacing missing records together with the reduced vital signs data using methods 1 and 2. The estimated mean and 95% CI results are displayed in Figures 8.2.1 to 8.2.3 for heart rate, systolic and diastolic blood pressure respectively. Figure 8.2.4 shows the estimated dietary response mean and 95% CI for the original data before imputing missing records and for data reduced using method 1 only. Tables 1a-d (Appendix A) show actual observed means for the original data and Tables 3a-d and 4a-c (Appendix A) show observed means for the reduced data using methods 1 and 2 respectively. See Figures 4.4.1-4.4.4 for plots of the actual mean and 95% CI plots for the original data. These plots

correspond to Figures 8.2.1A-8.2.4A, which show the model based mean and 95% CI for heart rate, systolic BP, diastolic BP and dietary response respectively. Comparisons of these plots show that the final model for the original data was a valid one. In each case, the plot of the estimated final mean model response for the original data (Figures 8.2.1A-8.2.4A) appears similar to the plots of the actual means on the original data (Figures 4.4.1-4.4.4). All final models appropriately describe the data since any estimated means were close to the observed means and were within the 95% CI bands (that were not too large).

8.2.1.1 Heart Rate

Table 8.1.1
Comparison of Models Fixed Effects for Mean Grouped Heart Rate (b/m)

Heart Rate	Centre	Drug	Base	Time	Time*Drug
Original Before Replaced	0.338	0.283	<0.001*	<0.001*	0.488
		0.272	<0.001*	<0.001*	0.487
Original After Replaced	0.378	0.327	<0.001*	<0.001*	0.428
		0.319	<0.001*	<0.001*	0.428
Average 2 Hours	0.545	0.899		<0.001*	0.252
	0.467	0.346	<0.001*	<0.001*	0.360
	0.544	0.794		<0.001*	
	0.467	0.116	<0.001*	<0.001*	
		0.769		<0.001*	
		0.116	<0.001*	<0.001*	
		0.900		<0.001*	0.252
		0.333	<0.001*	<0.001*	0.359
Average 3 Hours	0.195	0.898		<0.001*	0.107
	0.719	0.347	<0.001*	<0.001*	0.159
	0.195	0.644		<0.001*	
	0.719	0.098	<0.001*	<0.001*	
		0.583		<0.001*	
		0.097	<0.001*	<0.001*	
		0.900		<0.001*	0.106
		0.338	<0.001*	<0.001*	0.159

Note: Each row represents one of the various mixed models that were applied to the data. Each cell contains the p-values for the effects of covariates in the model.

Original Data:

The results both before and after imputing missing records gave similar findings, hence, only the results on the original data before imputing missing data will be considered. 'Centre' (p=0.338) was an insignificant effect in the model and can be removed. It can then be seen that there are no significant treatment differences (p=0.272).

Method 1: Averaging over 3 Time Points:

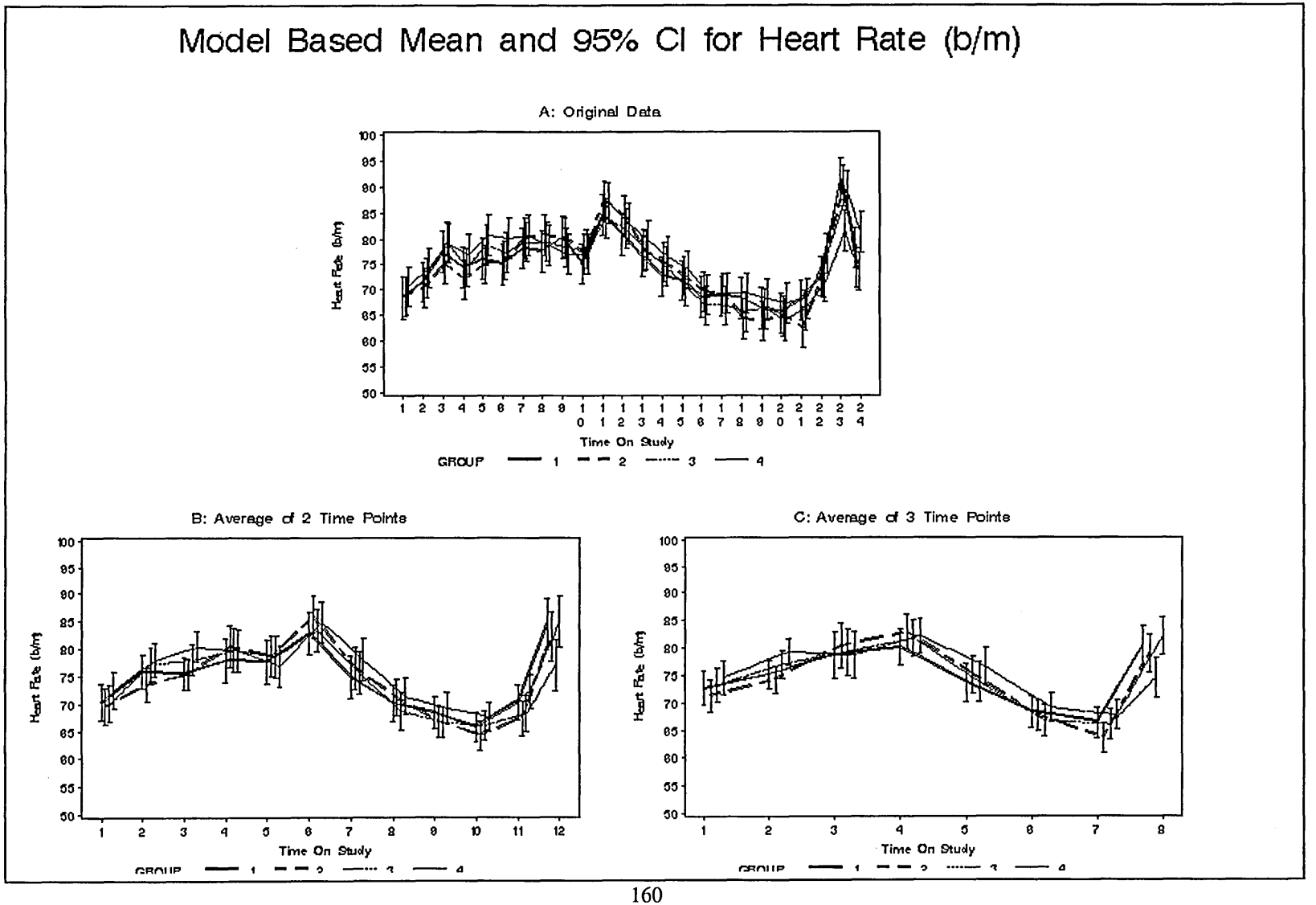
The 'interaction' ($p>0.106$) and the 'centre' term ($p>0.195$) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects ($p<0.001$ for both). The 'drug' effect also becomes more significant in the model ($p=0.097$). Finally, 'drug', 'base' and 'time' and the 'time' by 'treatment' interaction are all kept in the model. This is because the results for 'base' and 'time' do not change and 'drug' has the lowest significance. See Figure 8.2.1C for the final model based mean and 95% CI plot. There are no significant treatment differences ($p=0.338$).

Method 2: Averaging over 2 Time Points:

The 'interaction' ($p>0.252$) and the 'centre' term ($p>0.467$) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects ($p<0.001$ for both). The 'drug' effect also becomes more significant in the model ($p=0.116$). Finally, 'drug', 'base' and 'time' and the 'time' by 'treatment' interaction are all kept in the final model (see Figure 8.2.1B). This is because the results for 'base' and 'time' do not change and 'drug' has the lowest significance. There are no significant treatment differences ($p=0.333$).

NOTE: Both the reduced data structures (Figures 8.2.1B and C) have similar models and they appear similar to the original data model (Figure 8.2.1A). The original patterns in the data are maintained through the reduced models. No treatment differences were detected for any of the final models, agreeing with all test results and plots in the previous chapters. From the contrast comparisons in Table 20a (Appendix A) it can be seen that there were no individual treatment differences for any of the three data structures ($p>0.080$).

Figure 8.2.1


Model Based Mean and 95% CI for Heart Rate (b/m)
A: Original Data
Heart Rate (b/m)
Time On Study
GROUP 1 2 3 4
B: Average of 2 Time Points
Heart Rate (b/m)
Time On Study
C: Average of 3 Time Points
Heart Rate (b/m)
Time On Study

8.2.1.2 Systolic Blood Pressure

Table 8.1.2
Comparison of Models Fixed Effects for Mean Grouped Systolic Blood Pressure

Systolic BP	Centre	Drug	Base	Time	Time*Drug
Original Before Replaced	0.693	<0.001*	<0.001*	<0.001*	0.748
		<0.001*	<0.001*	<0.001*	0.748
Original After Replaced	0.621	<0.001*	<0.001*	<0.001*	0.922
		<0.001*	<0.001*	<0.001*	0.922
Average 2 Hours	0.534	0.014*		<0.001*	0.397
	0.659	<0.001*	<0.001*	<0.001*	0.320
	0.534	0.006*		<0.001*	
	0.660	<0.001*	<0.001*	<0.001*	
		0.006*		<0.001*	
		<0.001*	<0.001*	<0.001*	
		0.012*		<0.001*	0.396
		<0.001*	<0.001*	<0.001*	0.320
Average 3 Hours	0.540	0.014*		<0.001*	0.569
	0.672	<0.001*	<0.001*	<0.001*	0.490
	0.540	0.008*		<0.001*	
	0.672	<0.001*	<0.001*	<0.001*	
		0.007*		<0.001*	
		<0.001*	<0.001*	<0.001*	
		<0.001*		<0.001*	0.569
		<0.001*	<0.001*	<0.001*	0.489

Note: Each row represents one of the various mixed models that were applied to the data. Each cell contains the p-values for the effects of covariates in the model.

Original Data:

The results both before and after imputing missing records gave similar findings, hence, only the results on the original data before imputing missing data will be considered. 'Centre' ($p=0.693$) was an insignificant effect in the model and can be removed. It can then be seen that there were significant treatment differences ($p<0.001$).

Method 1: Averaging over 3 Time Points:

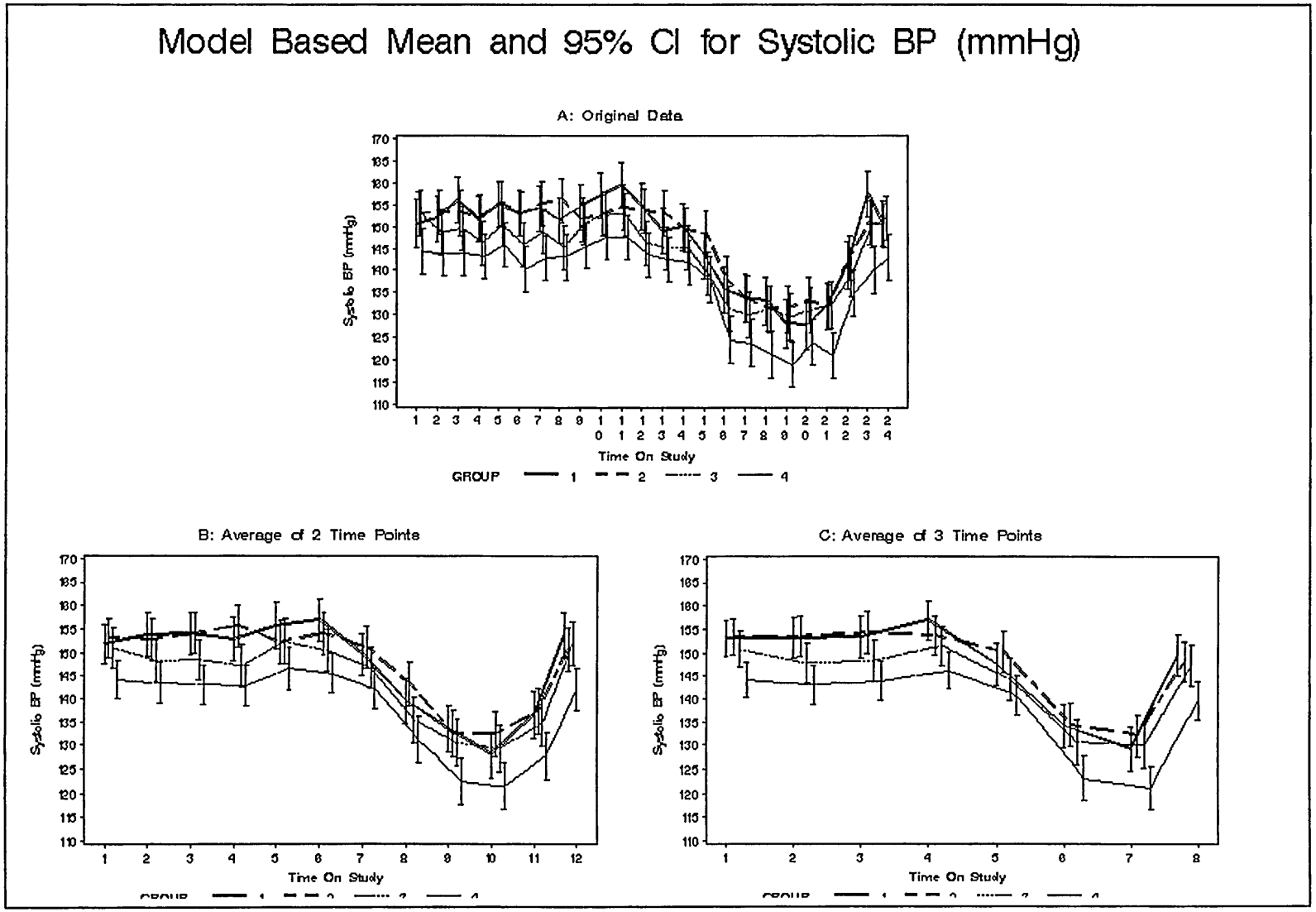
The 'interaction' ($p>0.489$) and the 'centre' term ($p>0.540$) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects ($p<0.001$ for both). The 'drug' effect is also most significant in this model ($p<0.001$) after removing just 'interaction', just 'centre' or 'both' terms. Finally, 'drug', 'base' and 'time' and the 'time' by 'drug' interaction are all kept for the final model. This is because the results for 'base' and 'time' do not change, 'drug' has no change in significance and all other effects are still highly insignificant. It can then be seen that there were significant treatment differences ($p<0.001$).

Method 2: Averaging over 2 Time Points:

The 'interaction' ($p>0.320$) and the 'centre' term ($p>0.534$) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects ($p<0.001$ for both). The 'drug' effect is also most significant in this model ($p<0.001$) after removing just interaction, just 'centre' or 'both' terms. 'Drug', 'base' and 'time' and the 'time' by 'drug' interaction are all kept for the final model. This is because the results for 'base', 'time' and 'drug' do not change and all other effects are highly insignificant. It can then be seen that there were significant treatment differences ($p<0.001$).

NOTE: Both the reduced data structures have similar models and agree with the findings for the original data. In all cases a 'drug' effect can be seen (Figures 8.2.2A-C). It appears as if drug 4 has the lowest mean systolic blood pressure response over time. From the contrast comparisons in Table 20b (Appendix A) it can be seen that there were differences in mean systolic blood pressure for drug 4 compared to all drugs 1, 2 and 3 for all three data structures ($p<0.006$ in all cases).

Figure 8.2.2


Model Based Mean and 95% CI for Systolic BP (mmHg)
A: Original Data
Systolic BP (mmHg)
Time On Study
GROUP 1 2 3 4
B: Average of 2 Time Points
Systolic BP (mmHg)
Time On Study
C: Average of 3 Time Points
Systolic BP (mmHg)
Time On Study

8.2.1.3 Diastolic Blood Pressure

Table 8.1.3
Comparison of Models Fixed Effects for Mean Grouped Diastolic Blood Pressure

Diastolic BP	Centre	Drug	Base	Time	Time*Drug
Original Before Replaced	0.487	<0.001*	<0.001*	<0.001*	0.175
		<0.001*	<0.001*	<0.001*	0.175
Original After Replaced	0.450	<0.001*	<0.001*	<0.001*	0.271
		<0.001*	<0.001*	<0.001*	0.271
Average 2 Hours	0.437	0.020*		<0.001*	0.129
	0.934	<0.001*	<0.001*	<0.001*	0.126
	0.438	0.018*		<0.001*	
	0.934	0.001*	<0.001*	<0.001*	
		0.024*		<0.001*	
		0.001*	<0.001*	<0.001*	
		0.019*		<0.001*	0.128
		<0.001*	<0.001*	<0.001*	0.125
Average 3 Hours	0.309	0.020*		<0.001*	0.358
	0.501	<0.001*	<0.001*	<0.001*	0.313
	0.309	0.026*		<0.001*	
	0.501	0.001*	<0.001*	<0.001*	
		0.027*		<0.001*	
		0.001*	<0.001*	<0.001*	
		0.019*		<0.001*	0.358
		<0.001*	<0.001*	<0.001*	0.312

Note: Each row represents one of the various mixed models that were applied to the data. Each cell contains the p-values for the effects of covariates in the model.

Original Data:

The results both before and after imputing missing records gave similar findings, hence, only the results on the original data before imputing missing data will be considered. 'Centre' (p=0.487) was an insignificant effect in the model and can be removed. It can then be seen that there were significant treatment differences (p<0.001).

Method 1: Averaging over 3 Time Points:

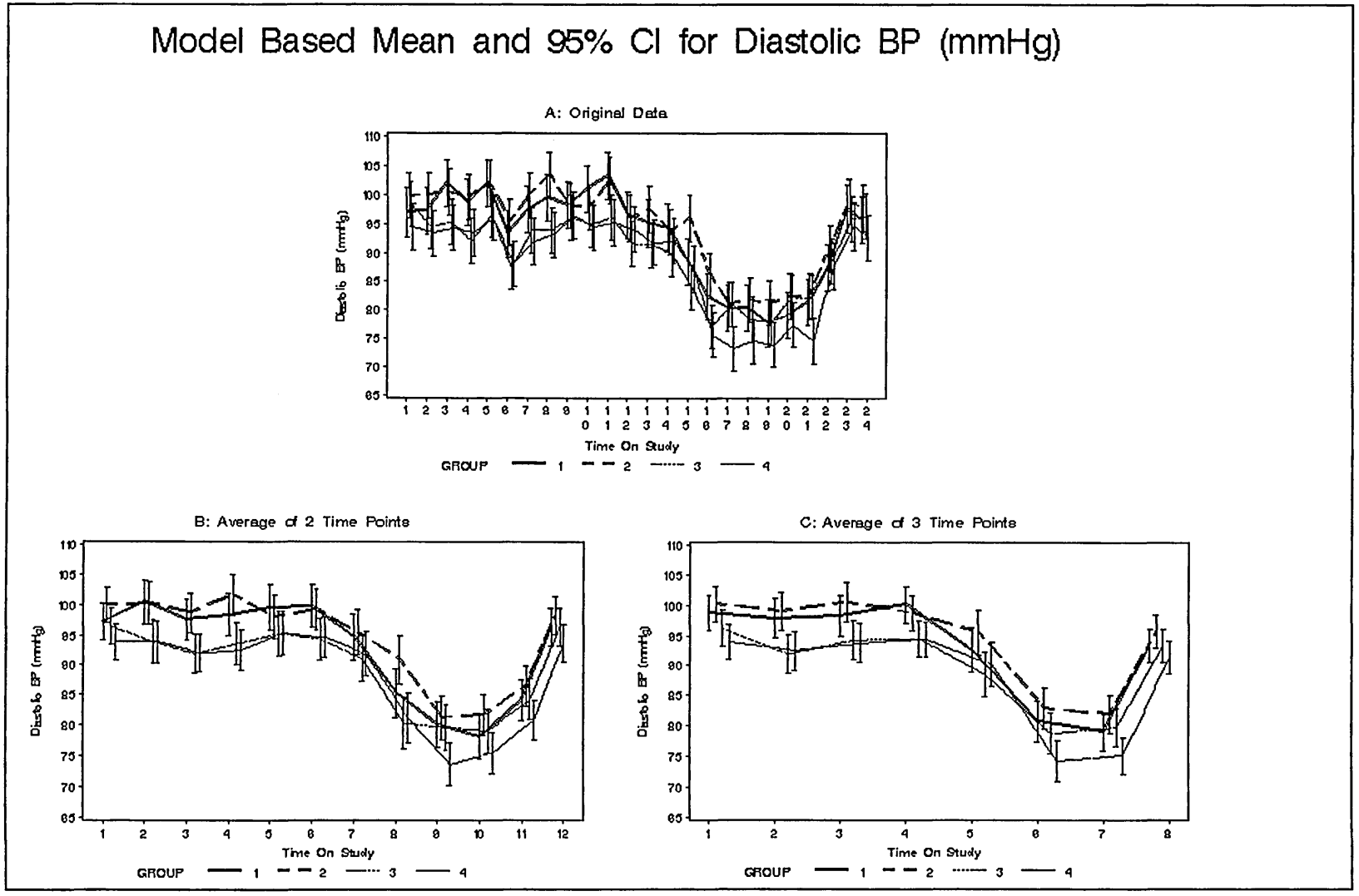
The 'interaction' (p>0.312) and the 'centre' term (p>0.309) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects (p<0.001 for both). The 'drug' effect is also most significant in this model (p<0.001) after removing just interaction, just centre or both terms. 'Drug', 'base' and 'time' effects and the 'time' by 'treatment' interaction are all kept in the final model. This is because the results for 'base', 'time' and 'drug' do not change and all other effects are highly insignificant. It can then be seen that there were significant treatment differences (p<0.001).

Method 2: Averaging over 2 Time Points:

The 'interaction' ($p>0.125$) and the 'centre' term ($p>0.437$) are both insignificant effects in the model. If both these terms are removed from the models, then there is no change in the 'time' and 'baseline' effects ($p<0.001$ for both). The 'drug' effect is also most significant in this model ($p<0.001$) after removing just 'interaction', just 'centre' or 'both' terms. The 'drug', 'base', 'time' and the 'time' by 'treatment' interaction are all kept in the final model. This is because the results for 'base', 'time' and 'drug' do not change and all other effects are not significant. It can then be seen that there were significant treatment differences ($p<0.001$).

NOTE: Both the reduced data structures have similar models. There is a significant treatment effect in the final model for all three data stuctures (Figures 8.2.3A-C). From the reduced data set plots (Figures 8.2.3B and C) it can be seen that drug 4 has the lowest mean diastolic blood pressure readings and drug 2 has the highest mean responses over the course of the study. These differences are not picked up as easily for the original data (Figure 8.2.3A). Comparisons of contrasts are displayed in Table 20c (Appendix A). It can be seen that there were differences in mean diastolic blood pressure for drug 1 compared to drug 4 ($p=0.004$ for all three data structures) and drug 2 compared with drug 4 ($p<0.001$ for all three data structures). Differences were also observed for drug 2 compared to drug 3 ($p<0.003$ for all three data structures). There was a difference between drug 1 and 3 for the original data ($p=0.045$) but this was not detected for the reduced data structures ($p>0.05$). It is believed that the results for the reduced data would be more robust since the assumption of asymptotic normality is met in this situation.

Figure 8.2.3


Model Based Mean and 95% CI for Diastolic BP (mmHg)
A: Original Data
Diastolic BP (mmHg)
Time On Study
GROUP 1 2 3 4
B: Average of 2 Time Points
Diastolic BP (mmHg)
Time On Study
GROUP 1 2 3 4
C: Average of 3 Time Points
Diastolic BP (mmHg)
Time On Study
GROUP 1 2 3 4

8.2.1.4 Dietary Response

Table 8.1.4
Comparison of Models Fixed Effects for Mean Grouped Dietary Response Data

Dietary Response	Group	Base	Time	Time*Group
Original Before Replaced	<0.001*	0.121	<0.001*	<0.001*
Original After Replaced	<0.001*	0.101	<0.001*	<0.001*
Average 3 Hours	<0.001*		0.100	<0.001*
	<0.001*	0.056	0.101	<0.001*
	<0.001*		0.196	
	<0.001*	0.056	0.197	

Note: Each row represents one of the various mixed models that were applied to the data. Each cell contains the p-values for the effects of covariates in the model.

Original Data:

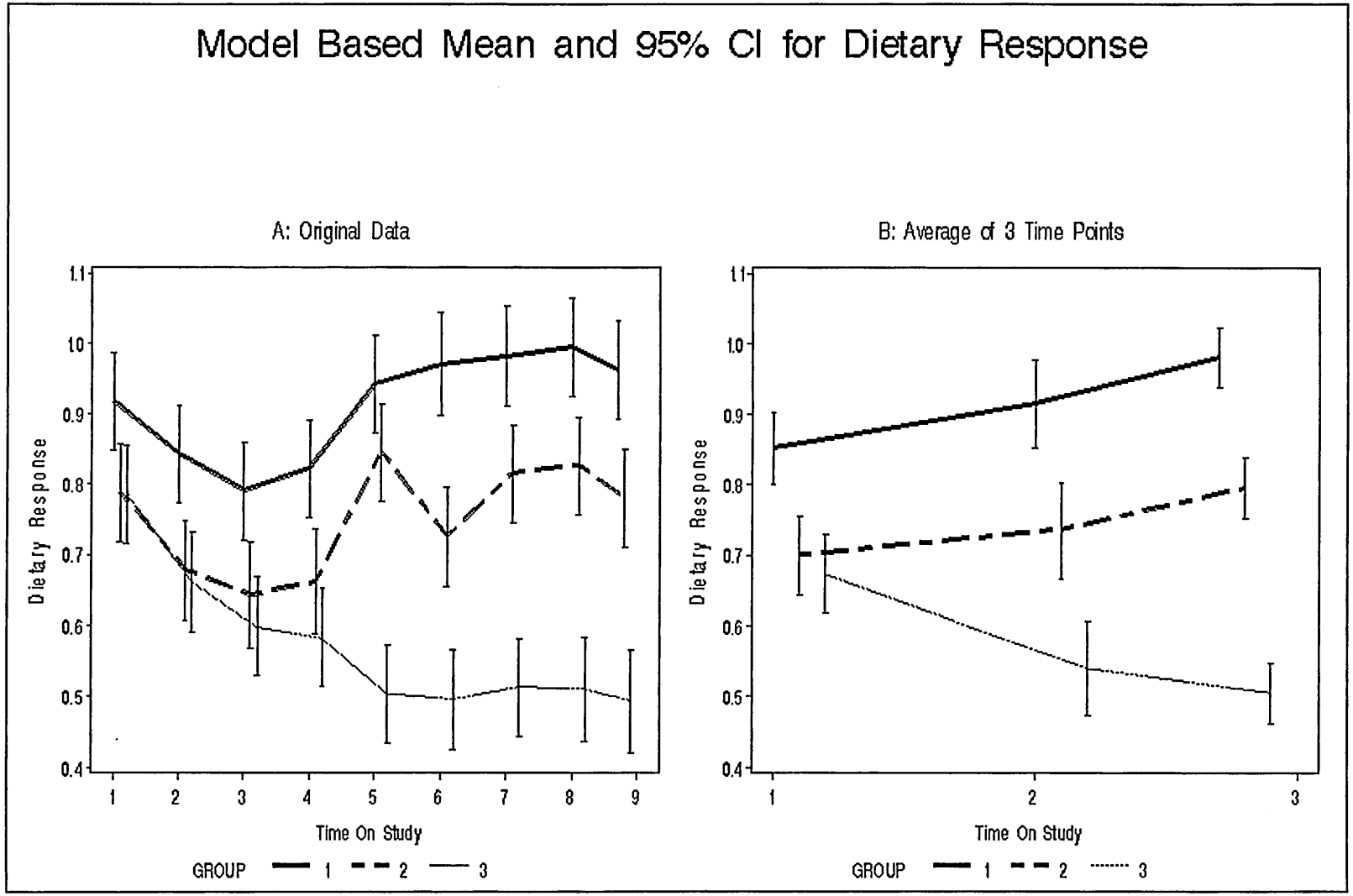
The results both before and after imputing missing records gave similar findings, hence, only the results on the original data before imputing missing data will be considered. It can then be seen that there were significant treatment differences ($p<0.001$).

Method 1: Averaging over 3 Time Points:

The interaction term ($p<0.001$) is an extremely significant effects in the model and therefore will not be dropped. 'Time' is insignificant ($p=0.101$) and 'baseline' measurement is borderline significant ($p=0.056$) for the full model. 'Group', 'base' and 'time' and 'time' by 'group' interaction were all kept in the final model. This is because the all terms were somehow describing the data. There were significant treatment differences ($p<0.001$).

NOTE: The reduced data structure has a similar model to the original data. There was a significant treatment effect in the final model for both data stuctures (Figures 8.2.4A-B). From the reduced data set plot (Figures 8.2.4B) it can be seen that therapy 3 has the lowest mean dietary response and therapy 1 had the highest mean response over the course of the study. These differences are not picked up as easily for the original data plot (Figure 8.2.4A). From the contrast comparisons in Table 20d (Appendix A) it can be seen that there were significant differences in mean dietary response for each therapy comparison for all three data structures ($p<0.001$ in all cases).

Figure 8.2.4


Model Based Mean and 95% CI for Dietary Response
A: Original Data
B: Average of 3 Time Points
Dietary Response
Time On Study
GROUP 1 2 3

8.3 Overview

Looking at the Kaplan-Meier time to event analysis plot for the first abnormal heart rate reading, drugs 4 and 3 seem to have the best and worst performances respectively. The drugs behave in a similar manner for systolic blood pressure also. However, for diastolic blood pressure, drug 1 and possibly drug 3 seem to have the best performances and drug 2 has the worst performance. Both the Log-rank and Wilcoxon tests do not reveal any significant differences between the treatment performances for the times to the first abnormally 'high' reading for any of the vital sign measurements.

Logistic regression analyses (with dichotomised categories of having either less than 50% or greater than or equal to 50% of abnormally high results and similarly of having less than 75% or greater than or equal to 75% of abnormally high results) were conducted. These analyses both indicate that the time-drug 'interaction' as well as the 'centre' term has no significant effect in the models. These terms are therefore considered to be non-influential in the models. The logistic models on the proportion of individuals with greater than or equal to 50% and 75% abnormality disagree with one another for diastolic blood pressure findings but do agree for systolic blood pressure results. The logistic analyses for greater than or equal to 75% abnormality gave comparable findings to the Chi-squared test results in Tables 16b and 16c (Appendix A) for both categorical systolic and diastolic blood pressure readings. The logistic analysis showed that there was a treatment difference between drugs 1 and 4 and also drugs 2 and 4 for systolic blood pressure, corresponding to the mixed modelling findings. However, no treatment difference was detected for proportion of individuals with greater than or equal to 75% abnormality for diastolic blood pressure, as with the survival analysis findings above. This finding does, however, contradict the results from the mixed model approach where differences in diastolic BP were noticed. Differences were detected between drugs 1 and 4 for the proportion of individuals with greater than or equal to 50% diastolic blood pressure abnormality and these differences were actually seen with the mixed modelling approach.

The mixed modelling approach (for reduced data using the approach of averaging either 2 or 3 successive observations respectively) was conducted on the data and these analyses indicated that the time-drug 'interaction' as well as the 'centre' term has no significant effect in the models. There are treatment differences for systolic and diastolic blood pressure as well as dietary response. Treatment differences were not detected for any heart rate data.

The mixed modelling approach was more sensitive to picking up data differences than the categorical data analyses approaches of time to event and logistic regression analyses that were conducted together with the Chi-squared tests for categorical data.

One should remember that the multivariate analysis assumes normality or robustness of tests; which may be OK in the case of averaging 3 successive observations (method 1), but may be questionable in the case of the averaging approach for 2 successive observations (method 2). Hence, it is believed that method 1 is more appropriate over method 2 to describe the data following data reduction.

It should also be mentioned that the present chapter does not consider in its study, the reduced data sets based on principal components and summary measures, since for these the information about the performances of various characteristics at different time points is lost.

It can be seen that for diastolic blood pressure, differences between drug 1 and 3 were not found for the reduced data but were seen for the original data only. The original data is studied here, but since the number of repeated measures is too large compared to the sample sizes there are serious doubts about the validity of any associated results, especially in the case of diastolic blood pressure, where differences in conclusion were noticed.

Hence, It was decided that data reduced using method 1 was the best format for the data to take in order for any multivariate testing to be conducted. This would allow the assumption of asymptotic normality without any further testing of the data and would lead to more robust test results than results on the original data. The multivariate mixed models approach of modelling the data was the optimal analysis methodology since it was more sensitive at picking up treatment differences than any other approach of those conducted. All the methods used for the categorical data analysis were not sensitive at picking up treatment differences when they actually existed.

CHAPTER 9: OVERVIEW

9.1 Discussion and Conclusions

Since the data were non-normal at some points and normal at others, it was decided to use robust [32] non-parametric or parametric statistical approaches as opposed to transforming the data. The result was to use the non-parametric Kruskal-Wallis approach, as well as parametric tests with a reduced number of repeated measurements p. The idea of using the Kruskal-Wallis tests was not to analyse the data at each repeated measurement, but was only used to compare the results both before and after imputing missing results. In all cases, tests on both data sets gave similar conclusions. This suggested that missing data generation was appropriate and would not distort the results that drastically for univariate testing. All univariate tests on the summary measures were conducted to compare treatments. The results both before and after imputing missing records gave similar conclusions; again suggesting that missing data generation was not distorting the results and also that data generation was not crucial in analysing the data in a univariate manner.

Mahalanobis distances were used to test for treatment differences between pairs of distances and also to compare results before and after data replacement for both the original and the reduced data sets. The findings before and after imputing missing records were similar for all data structures that were analysed. It was decided that the reduced average data and, possibly, the summary measures methods were the most appropriate data structures to describe the actual data. The principal component analysis (in all cases with significant initial results) was not a very useful approach for reducing the larger repeated measures data sets. The P.C.A. approach was only tested using the Mahalanobis distances and not using the multivariate modelling approaches.

The reduced data only after replacing missing records were analysed for all multivariate modelling to keep things consistent for both methods 1 and 2. This was since the same numbers of observations were available for each reduced data set following replacement of missing records.

In all cases, the best multivariate generalised mixed effects model for continuous data was after adjusting for 'baseline' readings and 'times'.

From the original data actual mean plots (Figures 4.4.1 to 4.4.3), it can be seen that the data peaks at two times, namely at 11 and 23 hours, for all vital sign measurements (heart rate, systolic and diastolic BP respectively). From observing this, it is suggested that the reasoning behind this could be that the

individuals are hungry or that some activity may be occurring at the particular time of drug administration.

All survival tests for time to the first abnormality showed insignificant treatment differences. This approach is not sensitive at picking up treatment differences and is subjective to what is considered to be an 'abnormality' in results.

The Chi-squared tests on the proportion of individuals having greater than or equal to 75% abnormality gave similar findings to the corresponding logistic regression models. These results agreed with the mixed model results for systolic blood pressure only, showing a treatment difference between drugs 4 and 1 and also drugs 4 and 2. However, the logistic regression results for greater than or equal to 75% abnormality did not agree with the mixed model findings for diastolic blood pressure showing no treatment differences as with the time to event analysis. The results for greater than or equal to 50% abnormality did agree with the mixed model findings for diastolic blood pressure showing a treatment difference between drugs 1 and 4. It is believed that the Chi-squared tests on categorical data are again dependent on the definition of 'abnormality' and hence the approach is unreliable to describe the data because of a lack of sensitivity. The logistic regression approach is also dependent on the definition of 'abnormality' but is more reliable than the Chi-squared approach, which in turn is more reliable than the time to event analysis. Of all multivariate analysis approaches, the mixed modelling approach was the most reliable and data sensitive method of analysing the data. The non-parametric testing approach of Mahalanobis distances was not as sensitive as the mixed modelling procedure. This was because not all treatment differences were detected when differences existed and some differences were detected when they may not be valid results due to the data being non-normal in nature.

The data reduction method 1 was the most reliable data reduction approach that still retained the element of time. The multivariate results obtained for this data set was more reliable than the results on the original data since asymptotic normality was met for the reduced data set.

There were no treatment differences for any of the summary measures for heart rate (beats/min). Treatment differences occurred for systolic blood pressure, diastolic blood pressures and also dietary response. For the vital signs analyses, the mean systolic and diastolic blood pressures responses for individuals on drug 4 were considerably lower than for any other treatments. For the dietary response data, there were significantly different mean responses between all three-therapy groups.

9.2 Further Work

- Time series approach could be applied.
- Covariance structure modelling could be attempted.
- There are other modelling procedures but only the generalised mixed effects model was selected for the primary analysis.
- The reasons for trends in the data could be due to external factors that aren't readily controllable such as whether an individual is taking other medications, whether the individual has eaten or not and when was drug administered. These are all things that influence the results of vital signs measurements in particular and could be used in the models if the information were available.
- Other variables could have been important in modelling the data. These are variables such as age. This was not available and therefore was not considered, however, it is definitely known to be a factor that would influence the heart rates for individuals.
- Multivariate normality could be tested using a regression approach (or other approaches that were suggested but not addressed).
- Zeger and Liang's GEE could be applied for multivariate analysis of repeated categorical data.
- The approaches in this thesis could be applied to other larger and smaller longitudinal data sets to see if the same conclusions could be obtained.

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APPENDIX A

Table 1a
Summary Statistics and Tests for Time and Drug
Original Data Set: Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	71.2	73.7	8.1	59.8	89.9	67.5	79.6	20	0.288	0.918
	2	75.7	73.7	10.4	48.7	97.3	65.5	79.6	21	0.354	
	3	73.7	72.8	12.5	46.2	92.9	65.8	83.4	22	0.531	
	4	72.8	72.0	6.2	63.1	86.3	68.1	75.2	21	0.348	
1	1	68.0	69.7	9.0	49.8	86.3	63.0	74.5	19	0.731	0.906
	2	67.8	68.5	9.6	47.8	83.5	62.0	75.6	22	0.762	
	3	70.5	67.8	10.6	46.2	85.0	65.4	73.8	21	0.357	
	4	71.3	69.8	6.8	53.5	80.5	67.4	74.3	21	0.179	
2	1	72.8	72.4	7.2	56.5	83.3	68.5	79.0	21	0.632	0.554
	2	69.0	70.1	12.7	50.8	97.3	60.8	79.5	22	0.422	
	3	70.5	71.3	13.0	48.8	94.0	66.3	77.3	21	0.531	
	4	76.0	73.5	10.1	54.5	87.5	68.3	81.2	21	0.088	
3	1	79.5	78.1	9.6	59.5	100.0	71.5	81.8	21	0.402	0.528
	2	74.7	74.0	11.6	51.8	94.7	67.3	83.8	21	0.829	
	3	81.3	78.5	16.2	49.3	106.0	70.5	88.5	21	0.661	
	4	78.7	78.3	10.1	56.7	92.3	74.0	86.8	21	0.144	
4	1	74.0	75.0	9.2	58.0	90.5	71.8	79.8	21	0.578	0.554
	2	71.6	71.8	11.2	50.3	93.0	65.0	79.3	22	0.936	
	3	76.1	74.3	14.2	43.8	95.0	65.3	86.8	22	0.197	
	4	76.3	76.3	8.5	57.3	90.5	71.3	83.8	21	0.863	
5	1	75.5	76.7	12.1	59.0	102.3	69.3	85.0	21	0.632	0.486
	2	75.6	74.8	11.2	50.0	94.0	66.3	81.8	22	0.845	
	3	79.8	78.7	15.1	46.0	106.3	67.5	88.0	22	0.973	
	4	79.8	79.9	8.8	63.3	100.0	75.0	84.5	21	0.977	
6	1	75.8	75.8	9.9	62.0	93.5	66.7	83.7	21	0.238	0.631
	2	75.8	75.7	11.2	51.5	97.0	67.0	84.8	22	0.959	
	3	76.1	77.2	15.2	45.8	100.3	65.3	90.3	22	0.506	
	4	79.8	79.4	8.3	65.8	97.5	74.3	85.8	21	0.897	
7	1	76.0	78.5	9.5	61.8	93.3	72.8	88.0	21	0.245	0.913
	2	78.3	80.5	14.1	52.8	120.3	71.5	89.0	22	0.177	
	3	83.7	79.3	16.7	47.5	102.3	68.0	91.3	22	0.123	
	4	78.8	79.9	11.4	67.7	121.3	73.5	82.0	21	0.000*	
8	1	74.0	77.6	12.9	60.5	109.8	68.5	80.8	21	0.089	0.693
	2	79.8	80.6	15.1	45.8	109.3	71.0	91.5	22	0.734	
	3	83.0	79.3	17.4	44.3	107.3	67.7	90.0	22	0.535	
	4	75.8	77.9	9.6	66.0	101.5	71.5	80.8	21	0.029*	
9	1	75.8	80.3	16.5	58.5	123.0	67.5	91.5	21	0.082	0.894
	2	76.8	80.3	20.1	44.3	145.0	68.0	90.0	22	0.014*	
	3	81.0	78.2	15.7	42.5	105.5	69.0	88.8	22	0.505	
	4	72.0	76.2	9.3	64.8	93.8	69.5	83.3	21	0.025*	
10	1	75.8	75.7	10.2	54.8	104.5	71.0	79.0	21	0.143	0.721
	2	77.5	77.1	12.4	50.3	99.5	68.3	89.0	22	0.704	
	3	82.6	78.0	13.4	51.0	96.5	67.4	87.8	22	0.098	
	4	77.0	76.2	8.4	55.8	92.0	71.3	80.8	21	0.608	
11	1	82.3	84.7	13.0	63.8	113.0	76.5	93.0	21	0.637	0.846
	2	87.2	88.4	13.2	65.3	118.7	78.0	94.8	22	0.884	
	3	83.9	83.8	17.0	49.7	107.8	76.3	99.5	22	0.152	
	4	85.3	86.0	9.6	73.0	105.7	80.5	91.3	21	0.266	
12	1	76.0	81.1	16.2	58.3	115.0	68.0	92.0	21	0.098	0.648
	2	85.9	85.2	14.8	56.7	108.8	72.8	94.0	22	0.570	
	3	82.4	81.8	17.9	51.7	118.5	72.3	96.5	22	0.751	
	4	81.5	82.3	8.4	63.5	94.0	77.7	89.0	21	0.224	

Table 1a cont.

Summary Statistics and Tests for Time and Drug

Original Data Set: Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
13	1	77.8	76.2	12.0	55.0	96.3	67.0	86.3	20	0.648	0.977
	2	77.0	77.9	15.5	47.0	109.0	69.0	85.0	21	0.917	
	3	77.8	77.8	16.5	45.0	109.5	67.5	88.5	22	0.958	
	4	77.0	78.9	12.3	66.0	113.0	73.5	82.0	21	0.000*	
14	1	73.0	72.8	9.2	54.0	90.5	65.5	78.0	21	0.815	0.724
	2	77.0	76.2	12.6	47.0	107.0	70.0	84.0	22	0.823	
	3	73.0	74.7	15.9	43.0	113.0	65.5	84.0	21	0.827	
	4	74.5	75.7	8.4	64.0	93.5	69.0	79.0	21	0.182	
15	1	70.0	72.1	11.9	51.5	100.5	66.0	75.0	21	0.038*	0.866
	2	67.8	73.1	14.4	48.5	102.5	64.0	82.0	22	0.125	
	3	68.3	70.3	11.3	51.3	92.0	62.5	76.5	22	0.531	
	4	71.0	73.1	11.2	54.5	106.5	67.0	75.5	21	0.016*	
16	1	70.0	69.4	8.4	54.0	89.5	63.0	75.0	21	0.901	0.843
	2	67.3	69.6	14.1	46.0	104.0	60.5	82.5	22	0.490	
	3	66.0	66.8	11.3	44.5	87.0	60.5	73.5	22	0.747	
	4	66.0	68.2	9.4	50.0	88.0	62.0	71.0	21	0.108	
17	1	69.5	69.3	7.4	55.5	83.0	63.0	75.0	21	0.946	0.868
	2	68.0	69.4	12.5	45.0	94.0	61.0	76.5	22	0.903	
	3	67.3	66.7	11.0	42.5	86.0	61.0	73.0	22	0.690	
	4	67.0	68.5	8.5	53.0	86.5	62.5	73.5	21	0.655	
18	1	67.5	68.6	8.3	54.0	82.0	62.3	77.3	20	0.475	0.431
	2	62.5	64.6	10.3	47.5	85.5	57.0	73.0	22	0.704	
	3	66.3	65.8	10.9	40.0	82.0	61.5	73.5	20	0.341	
	4	66.5	68.5	6.7	56.5	82.5	64.0	73.0	21	0.862	
19	1	66.3	66.7	7.3	49.5	78.0	62.5	72.0	20	0.639	0.855
	2	65.5	64.3	9.6	44.0	79.0	57.5	72.5	22	0.656	
	3	68.3	66.4	11.0	45.5	84.5	60.3	73.3	20	0.768	
	4	65.5	67.3	7.4	53.0	82.0	63.0	70.0	21	0.724	
20	1	64.5	66.0	8.6	54.0	85.0	61.0	71.0	21	0.390	0.782
	2	63.3	65.0	11.8	45.0	95.0	56.0	70.5	22	0.257	
	3	64.3	64.3	10.4	41.5	80.0	57.5	73.5	20	0.525	
	4	65.5	66.4	4.8	57.5	75.0	63.5	70.0	21	0.671	
21	1	66.0	68.6	8.9	55.5	94.0	62.0	75.0	21	0.082	0.245
	2	60.5	62.6	9.7	45.0	83.0	55.5	69.0	22	0.384	
	3	69.5	66.1	11.6	40.5	84.0	61.0	76.0	21	0.528	
	4	65.0	67.3	10.3	57.0	106.5	64.5	67.5	21	0.000*	
22	1	75.0	72.9	11.7	52.5	100.0	62.5	80.0	21	0.568	0.664
	2	69.8	72.3	15.6	43.5	103.5	60.0	82.5	22	0.573	
	3	71.5	71.5	15.6	45.0	111.0	60.0	85.0	21	0.525	
	4	73.8	75.8	11.9	61.0	102.5	67.0	85.5	20	0.112	
23	1	91.6	91.1	15.6	59.5	118.0	78.6	103.3	20	0.939	0.250
	2	81.8	89.5	25.7	50.3	173.0	74.3	101.3	22	0.006*	
	3	78.8	81.1	14.8	51.0	105.0	75.7	89.0	21	0.438	
	4	84.3	87.7	12.0	72.5	122.7	79.0	95.0	19	0.024*	
24	1	77.0	78.4	10.2	61.8	102.0	71.5	83.0	21	0.626	0.141
	2	72.7	74.1	10.0	54.5	94.0	69.0	77.8	22	0.299	
	3	74.0	73.4	12.6	47.0	104.7	68.0	81.7	22	0.714	
	4	78.5	80.5	12.5	60.5	105.7	76.8	88.3	21	0.167	

Table 1b

Summary Statistics and Tests for Time and Drug

Original Data Set: Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	149.7	151.3	12.1	128.4	174.4	143.1	158.8	20	0.968	0.857
	2	146.8	148.7	11.1	128.5	177.6	143.2	154.1	21	0.385	
	3	147.2	152.3	14.1	129.9	179.6	144.5	166.5	22	0.041*	
	4	149.0	149.1	13.6	128.5	167.3	139.8	162.6	21	0.066	
1	1	153.5	153.1	14.3	127.3	178.0	143.3	162.5	19	0.794	0.038*
	2	150.8	151.4	12.7	122.0	170.0	144.8	163.8	22	0.278	
	3	154.8	154.2	18.9	99.4	184.0	145.4	166.2	21	0.150	
	4	143.0	143.3	11.6	125.0	168.5	137.8	149.3	21	0.808	
2	1	153.5	153.9	13.9	127.0	177.8	146.0	164.8	21	0.864	0.110
	2	149.1	152.5	12.2	129.5	172.3	143.8	162.6	22	0.416	
	3	146.5	149.8	16.3	107.5	183.3	141.8	161.5	21	0.425	
	4	145.5	142.9	14.0	111.3	166.2	132.5	152.0	21	0.727	
3	1	162.3	158.2	16.6	122.5	185.5	142.3	170.8	21	0.374	0.015*
	2	150.3	152.2	14.4	127.3	188.0	145.7	157.5	21	0.327	
	3	152.3	150.7	14.2	115.0	176.7	144.3	157.0	21	0.624	
	4	146.5	142.9	11.1	122.0	158.5	131.3	150.3	21	0.025*	
4	1	155.3	154.6	16.9	125.0	196.8	140.3	159.5	21	0.633	0.186
	2	149.1	151.3	15.1	130.3	178.8	137.8	160.3	22	0.089	
	3	148.8	147.9	16.9	96.3	177.0	140.8	155.5	22	0.057	
	4	142.0	142.1	15.2	112.5	166.8	138.0	151.5	21	0.426	
5	1	157.0	157.0	14.6	125.8	184.0	150.5	165.5	21	0.947	0.033*
	2	152.0	153.9	13.7	124.5	179.5	145.3	165.7	22	0.990	
	3	152.6	152.1	15.7	109.3	193.8	144.3	157.3	22	0.071	
	4	147.3	144.8	12.5	117.8	169.8	139.0	152.7	21	0.922	
6	1	154.0	156.0	17.3	119.5	198.5	144.8	163.3	21	0.149	0.005*
	2	150.7	150.9	12.3	124.5	174.0	140.8	157.3	22	0.856	
	3	147.4	147.5	19.2	108.0	186.3	137.5	156.5	22	0.901	
	4	138.5	139.3	13.3	116.0	169.0	132.0	146.5	21	0.752	
7	1	158.0	156.6	19.2	116.0	192.0	143.0	166.5	21	0.690	0.023*
	2	151.4	153.5	11.9	129.3	178.5	144.0	161.8	22	0.985	
	3	149.9	150.4	14.5	109.7	176.5	143.7	158.3	22	0.335	
	4	144.3	141.8	12.7	120.8	166.0	133.0	150.0	21	0.465	
8	1	149.0	153.3	16.6	118.8	184.3	142.0	164.0	21	0.483	0.039*
	2	147.7	154.1	16.7	118.8	187.0	143.3	168.3	22	0.214	
	3	146.8	146.8	16.5	100.3	173.3	138.0	158.3	22	0.193	
	4	139.8	142.0	15.4	118.0	178.0	131.5	152.3	21	0.502	
9	1	159.8	156.7	16.8	120.8	185.5	146.0	163.7	21	0.786	0.150
	2	148.4	150.2	15.4	123.3	182.0	137.8	163.7	22	0.902	
	3	154.1	152.4	17.4	112.8	186.8	138.3	162.8	22	0.963	
	4	144.8	144.7	14.9	116.0	169.5	135.0	154.7	21	0.815	
10	1	159.5	159.4	14.5	124.8	189.5	148.8	170.5	21	0.839	0.054
	2	150.3	151.7	13.6	127.8	178.0	140.7	160.8	22	0.449	
	3	154.8	154.7	20.3	100.3	193.0	142.8	167.0	22	0.506	
	4	148.3	146.5	13.1	125.8	173.5	134.3	155.3	21	0.317	
11	1	163.8	161.7	17.7	125.3	192.0	154.0	170.0	21	0.748	0.059
	2	150.8	153.9	18.7	115.3	184.0	145.3	169.8	22	0.343	
	3	153.3	154.4	17.0	116.3	191.8	144.5	162.8	22	0.986	
	4	148.5	146.5	15.1	121.7	168.8	133.3	158.0	21	0.219	
12	1	157.5	156.6	18.8	118.0	184.0	142.3	176.0	21	0.538	0.053
	2	150.6	153.0	16.0	122.0	187.5	142.0	162.7	22	0.884	
	3	148.2	147.9	17.2	111.0	181.5	140.0	158.0	22	0.711	
	4	145.3	142.5	11.6	124.0	165.7	133.0	150.5	21	0.264	

Table 1b cont.

Summary Statistics and Tests for Time and Drug

Original Data Set: Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
13	1	149.5	151.2	17.1	115.5	177.5	141.0	164.5	20	0.649	0.120
	2	150.0	152.2	17.5	116.0	196.5	145.5	161.0	21	0.473	
	3	148.3	146.7	18.3	105.0	186.0	133.5	157.5	22	0.996	
	4	144.0	141.4	14.4	114.5	175.5	135.5	148.0	21	0.536	
14	1	151.5	152.1	12.4	129.0	180.0	146.0	159.0	21	0.890	0.082
	2	150.0	148.8	15.4	118.5	174.0	139.0	163.0	22	0.539	
	3	145.0	147.5	20.2	95.0	186.5	137.0	160.0	21	0.421	
	4	141.5	140.9	14.2	114.0	166.0	133.0	148.5	21	0.786	
15	1	145.0	145.8	18.5	108.5	181.0	136.0	156.5	21	0.935	0.154
	2	146.3	147.0	15.6	117.0	172.0	141.0	159.5	22	0.234	
	3	135.8	140.9	19.7	96.0	187.0	131.0	154.0	22	0.782	
	4	140.5	136.9	13.4	114.0	160.0	124.0	148.5	21	0.139	
16	1	136.5	138.1	17.6	115.0	192.0	127.0	144.0	21	0.006*	0.002*
	2	138.5	136.9	15.2	99.0	160.0	131.0	146.0	22	0.221	
	3	129.0	133.0	16.2	112.5	183.5	122.5	138.0	22	0.002*	
	4	122.5	123.5	11.2	102.5	148.5	115.5	132.5	21	0.662	
17	1	139.5	136.1	17.8	98.5	175.0	124.0	145.5	21	0.921	0.037*
	2	133.8	133.8	14.3	106.0	166.0	126.0	139.0	22	0.179	
	3	129.8	131.6	14.4	105.0	162.0	121.5	142.0	22	0.690	
	4	125.0	122.8	14.7	103.0	160.5	109.5	133.5	21	0.189	
18	1	132.0	135.0	18.1	108.0	179.0	121.8	143.8	20	0.359	0.049*
	2	132.8	131.1	13.8	107.0	154.0	119.5	140.0	22	0.492	
	3	129.8	134.4	21.7	102.0	193.5	118.3	147.3	20	0.205	
	4	115.5	120.2	15.6	91.0	144.5	110.0	136.5	21	0.167	
19	1	125.8	129.7	21.0	91.5	187.5	117.8	137.0	20	0.056	0.023*
	2	131.8	130.3	10.8	113.0	148.0	120.0	138.0	22	0.087	
	3	131.8	132.6	19.4	90.5	169.5	121.3	139.8	20	0.733	
	4	118.3	117.9	14.5	84.5	141.0	110.0	128.0	21	0.838	
20	1	128.5	130.7	19.9	97.0	176.0	115.0	139.0	21	0.282	0.199
	2	132.5	131.9	15.2	104.0	180.5	121.0	140.5	22	0.016*	
	3	134.0	134.1	17.4	103.0	166.0	120.8	144.8	20	0.909	
	4	123.5	122.9	14.7	83.0	147.0	114.0	133.0	21	0.379	
21	1	134.5	134.5	18.1	111.0	175.0	121.5	141.0	21	0.175	0.016*
	2	130.0	130.6	13.1	106.0	165.5	122.0	134.0	22	0.034*	
	3	133.0	134.5	18.4	99.0	166.5	124.0	148.0	21	0.514	
	4	118.5	119.9	14.6	96.0	146.5	111.0	129.0	21	0.464	
22	1	135.0	143.6	21.6	117.5	196.5	129.5	152.5	21	0.018*	0.398
	2	144.0	142.3	16.2	117.5	179.5	133.0	152.0	22	0.343	
	3	141.5	141.3	20.2	98.5	176.0	132.5	156.5	21	0.811	
	4	134.8	133.2	16.8	101.5	166.0	120.3	146.5	20	0.922	
23	1	157.5	158.6	20.4	129.0	203.0	147.9	171.0	20	0.430	0.003*
	2	153.8	150.1	14.3	120.0	177.0	143.3	158.5	22	0.242	
	3	151.0	150.4	21.5	91.0	183.3	140.0	163.0	21	0.308	
	4	138.5	137.8	11.7	112.7	154.0	128.5	148.5	19	0.455	
24	1	153.3	152.4	15.5	119.5	179.7	143.8	162.3	21	0.982	0.041*
	2	147.1	149.1	11.6	124.3	178.0	141.3	155.5	22	0.422	
	3	152.0	153.6	19.7	120.5	201.5	137.3	160.7	22	0.027*	
	4	141.0	142.0	14.1	122.0	182.0	132.0	150.0	21	0.091	

Table 1c

Summary Statistics and Tests for Time and Drug

Original Data Set: Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	97.5	96.9	6.8	82.1	111.3	92.4	100.2	20	0.995	0.900
	2	96.4	95.0	5.9	82.2	103.9	92.8	99.4	21	0.128	
	3	94.8	96.3	7.8	83.9	112.0	91.3	102.7	22	0.528	
	4	95.1	95.6	8.7	81.8	113.0	89.5	99.0	21	0.425	
1	1	97.8	98.1	9.1	81.3	115.8	93.8	104.3	19	0.799	0.173
	2	99.4	99.2	9.0	81.3	115.4	94.0	105.6	22	0.964	
	3	100.8	98.1	10.6	67.6	114.0	93.7	105.5	21	0.078	
	4	95.0	94.2	6.8	82.0	105.3	91.0	99.3	21	0.540	
2	1	100.5	98.2	10.0	82.0	115.3	90.0	106.8	21	0.536	0.145
	2	98.5	99.6	10.5	81.8	123.8	93.0	106.0	22	0.859	
	3	92.8	94.2	9.6	76.3	111.0	88.3	103.0	21	0.689	
	4	93.5	93.1	8.6	77.0	109.0	87.8	98.0	21	0.981	
3	1	104.5	103.0	10.6	80.8	115.3	96.8	112.8	21	0.061	0.019*
	2	101.8	100.3	11.3	74.7	121.3	90.8	106.2	21	0.699	
	3	94.0	95.0	10.8	77.8	113.0	87.0	104.0	21	0.378	
	4	90.5	94.0	9.8	80.0	115.0	87.0	99.3	21	0.305	
4	1	100.5	100.3	10.7	80.3	116.5	94.8	106.0	21	0.475	0.062
	2	101.3	99.4	11.2	75.8	123.0	91.8	107.8	22	0.992	
	3	93.6	92.3	10.7	68.3	108.3	86.3	101.5	22	0.461	
	4	97.6	93.2	10.9	69.3	110.5	86.5	100.0	21	0.200	
5	1	105.3	103.2	9.9	81.8	118.0	99.0	110.5	21	0.094	0.035*
	2	99.5	101.8	10.7	87.5	132.5	93.8	109.8	22	0.068	
	3	96.5	96.8	11.0	69.0	114.5	91.0	106.0	22	0.427	
	4	94.3	95.8	7.2	83.0	109.3	91.5	101.0	21	0.594	
6	1	93.0	94.8	9.7	74.0	112.8	90.8	103.3	21	0.497	0.017*
	2	93.5	94.6	10.0	80.0	119.0	86.0	101.0	22	0.091	
	3	85.9	87.7	9.2	67.0	103.3	82.3	95.0	22	0.450	
	4	88.3	87.8	8.2	71.3	106.8	82.0	91.7	21	0.695	
7	1	99.5	98.3	11.8	73.0	121.3	94.7	106.8	21	0.621	0.019*
	2	98.3	99.0	7.8	86.3	119.5	93.0	103.0	22	0.408	
	3	93.5	94.1	9.3	74.7	113.5	89.0	99.5	22	0.721	
	4	94.0	91.7	7.7	76.0	102.0	85.5	98.5	21	0.244	
8	1	100.5	100.2	9.4	77.8	113.5	95.0	106.0	21	0.513	0.004*
	2	102.5	102.6	11.8	82.3	133.7	98.0	108.0	22	0.227	
	3	93.6	94.1	10.2	75.0	113.7	85.8	98.3	22	0.833	
	4	91.0	92.8	7.8	81.5	109.8	88.3	97.3	21	0.099	
9	1	99.7	99.4	10.2	81.5	116.8	91.3	108.8	21	0.664	0.673
	2	97.5	97.5	9.6	79.3	114.8	91.3	105.3	22	0.821	
	3	95.4	96.4	10.9	75.3	114.3	89.5	103.5	22	0.610	
	4	95.3	96.2	11.6	79.0	125.5	90.0	101.0	21	0.446	
10	1	102.8	102.2	10.2	80.0	122.0	97.8	108.8	21	0.503	0.019*
	2	97.2	97.8	6.6	88.0	111.8	93.3	102.5	22	0.338	
	3	95.4	95.1	11.6	63.0	117.5	90.0	99.0	22	0.061	
	4	93.8	94.1	9.3	77.5	110.7	87.3	97.8	21	0.545	
11	1	108.0	104.6	13.0	76.3	124.0	99.0	114.0	21	0.496	0.033*
	2	102.1	103.5	13.4	86.5	140.0	93.3	109.0	22	0.045*	
	3	94.9	96.4	10.9	78.5	113.0	89.3	104.3	22	0.247	
	4	93.5	94.9	10.9	75.0	117.3	88.3	100.6	21	0.743	
12	1	104.3	97.5	14.3	60.3	117.0	92.3	106.5	21	0.030*	0.204
	2	96.5	96.2	9.9	78.3	117.0	90.7	102.7	22	0.299	
	3	90.9	91.8	10.1	73.0	108.0	84.0	100.3	22	0.599	
	4	93.5	93.7	9.5	74.8	114.0	90.0	98.0	21	0.676	

Table 1c cont.

Summary Statistics and Tests for Time and Drug

Original Data Set: Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
13	1	98.0	96.0	12.1	66.0	120.5	88.0	100.8	20	0.415	0.276
	2	98.0	96.7	10.2	72.5	113.0	91.0	103.0	21	0.810	
	3	92.3	91.6	11.7	70.0	110.5	85.0	99.0	22	0.366	
	4	94.0	91.5	11.3	69.0	108.5	83.0	97.0	21	0.415	
14	1	94.8	95.2	9.8	77.0	110.5	88.5	104.0	21	0.538	0.521
	2	92.8	93.6	14.0	66.0	114.0	86.5	103.0	22	0.166	
	3	93.5	90.5	14.0	56.5	113.0	84.0	99.5	21	0.166	
	4	89.0	91.7	11.8	77.5	122.5	83.0	96.0	21	0.017*	
15	1	90.5	89.8	16.1	56.5	112.5	84.0	100.0	21	0.248	0.095
	2	95.8	95.6	15.1	69.0	121.5	79.5	107.0	22	0.602	
	3	86.5	84.3	12.8	51.0	106.0	81.5	91.5	22	0.060	
	4	85.0	86.9	12.1	64.5	112.5	80.0	91.5	21	0.810	
16	1	81.5	84.2	12.0	70.0	119.0	78.0	89.5	21	0.011*	0.006*
	2	82.5	85.4	12.0	63.0	107.5	78.0	98.0	22	0.691	
	3	75.8	77.3	10.0	58.0	97.5	70.5	84.5	22	0.809	
	4	74.0	75.3	9.4	57.0	95.5	70.5	79.0	21	0.626	
17	1	80.0	81.8	10.4	55.5	100.5	78.5	91.0	21	0.143	0.070
	2	80.8	81.4	10.0	66.0	104.5	74.0	89.5	22	0.752	
	3	82.3	81.2	12.0	58.5	101.0	72.5	90.5	22	0.831	
	4	71.5	72.8	13.3	49.5	99.0	66.0	81.5	21	0.928	
18	1	80.5	82.3	13.0	61.5	107.5	76.0	89.3	20	0.400	0.151
	2	81.0	81.8	10.3	62.5	100.0	74.5	89.5	22	0.521	
	3	80.3	79.4	12.4	62.0	101.5	68.8	90.5	20	0.320	
	4	70.0	74.1	13.5	54.5	97.5	65.5	86.0	21	0.060	
19	1	79.5	79.8	13.8	49.0	113.0	73.0	86.3	20	0.330	0.216
	2	80.8	81.1	9.5	66.0	97.5	74.0	88.0	22	0.213	
	3	78.5	79.0	12.7	51.0	107.0	69.0	87.0	20	0.962	
	4	73.0	73.5	11.7	48.5	95.5	68.0	82.0	21	0.998	
20	1	78.5	81.0	12.8	57.0	108.5	74.5	86.5	21	0.340	0.327
	2	82.0	81.8	7.2	70.5	103.5	77.5	84.0	22	0.025*	
	3	82.8	83.3	12.3	64.0	113.0	74.3	89.8	20	0.748	
	4	74.5	77.1	13.7	42.0	106.5	71.5	84.0	21	0.244	
21	1	82.5	82.8	9.1	70.0	108.0	78.0	87.0	21	0.111	0.018*
	2	82.3	82.0	7.8	69.0	102.5	78.0	86.0	22	0.480	
	3	83.0	82.8	12.5	58.5	110.0	73.0	88.0	21	0.897	
	4	72.5	74.2	11.5	56.0	99.0	67.5	76.5	21	0.071	
22	1	87.5	89.0	11.9	69.5	111.0	83.0	97.5	21	0.294	0.882
	2	89.5	90.8	10.7	72.5	108.5	83.0	96.5	22	0.539	
	3	90.5	89.1	14.8	62.5	119.0	77.5	101.0	21	0.946	
	4	88.5	87.6	13.3	65.0	110.0	76.5	98.0	20	0.656	
23	1	98.8	98.6	13.0	76.0	124.5	90.5	105.6	20	0.660	0.430
	2	100.3	98.2	10.4	66.0	115.3	92.0	104.3	22	0.032*	
	3	96.5	96.1	12.2	58.0	112.3	87.7	106.0	21	0.015*	
	4	93.0	93.7	9.8	74.0	109.0	87.0	100.0	19	0.789	
24	1	96.8	97.0	10.6	77.5	115.7	92.3	104.5	21	0.499	0.156
	2	96.4	97.2	7.1	86.7	113.3	92.3	101.5	22	0.472	
	3	95.3	96.6	8.6	81.5	117.0	92.0	102.0	22	0.786	
	4	92.0	92.3	8.7	79.0	113.8	85.0	96.0	21	0.151	

Table 1d
Summary Statistics and Tests by Time and Therapy
Original Data Set: Dietary Response

TIME	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	Group1	0.9	1.0	0.1	0.8	1.1	0.9	1.0	8	0.835	0.539
	Group2	1.0	1.0	0.1	0.8	1.1	0.9	1.1	8	0.744	
	Group3	1.0	1.0	0.1	0.9	1.1	1.0	1.1	8	0.664	
1	Group1	0.9	0.9	0.1	0.7	1.1	0.8	1.0	8	0.952	0.077
	Group2	0.8	0.8	0.1	0.6	0.9	0.7	0.9	8	0.992	
	Group3	0.8	0.8	0.1	0.6	0.9	0.8	0.8	8	0.335	
2	Group1	0.8	0.8	0.1	0.6	1.0	0.8	1.0	8	0.350	0.009*
	Group2	0.7	0.7	0.1	0.6	0.7	0.6	0.7	8	0.372	
	Group3	0.7	0.7	0.1	0.5	0.8	0.6	0.7	8	0.887	
3	Group1	0.8	0.8	0.1	0.7	0.9	0.7	0.8	8	0.795	0.010*
	Group2	0.7	0.6	0.1	0.5	0.7	0.5	0.7	7	0.109	
	Group3	0.6	0.6	0.1	0.5	0.8	0.5	0.6	8	0.103	
4	Group1	0.8	0.8	0.1	0.7	0.9	0.8	0.9	8	0.231	0.007*
	Group2	0.6	0.7	0.2	0.5	0.9	0.5	0.8	7	0.665	
	Group3	0.6	0.6	0.1	0.4	0.8	0.5	0.6	8	0.815	
5	Group1	0.9	0.9	0.1	0.7	1.1	0.9	1.0	8	0.866	<0.001*
	Group2	0.9	0.8	0.1	0.7	1.0	0.8	0.9	8	0.856	
	Group3	0.5	0.5	0.1	0.4	0.7	0.4	0.6	8	0.786	
6	Group1	1.0	1.0	0.2	0.8	1.1	0.8	1.1	7	0.069	<0.001*
	Group2	0.7	0.7	0.1	0.6	0.9	0.7	0.8	8	0.844	
	Group3	0.5	0.5	0.0	0.4	0.5	0.5	0.5	8	0.032*	
7	Group1	1.0	1.0	0.1	0.9	1.1	0.9	1.1	8	0.277	<0.001*
	Group2	0.8	0.8	0.1	0.7	0.9	0.7	0.9	8	0.376	
	Group3	0.5	0.5	0.0	0.5	0.6	0.5	0.5	8	0.151	
8	Group1	1.0	1.0	0.1	0.8	1.2	0.9	1.1	8	0.844	<0.001*
	Group2	0.8	0.8	0.1	0.7	1.0	0.8	0.9	8	0.755	
	Group3	0.5	0.5	0.1	0.4	0.6	0.5	0.6	7	0.729	
9	Group1	1.0	1.0	0.1	0.8	1.1	0.9	1.0	8	0.074	<0.001*
	Group2	0.8	0.8	0.1	0.7	0.9	0.7	0.9	8	0.399	
	Group3	0.5	0.5	0.0	0.5	0.5	0.5	0.5	7	0.755	

Table 2a
Summary Statistics and Tests for Time and Drug
After Data Replaced: Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	71.2	73.7	8.1	59.8	89.9	67.5	79.6	20	0.288	0.921
	2	75.7	73.7	10.4	48.7	97.3	65.5	79.6	21	0.354	
	3	73.7	72.2	12.2	46.2	89.9	66.0	82.5	20	0.280	
	4	72.8	72.0	6.2	63.1	86.3	68.1	75.2	21	0.348	
1	1	69.3	70.5	8.9	49.8	86.3	64.5	74.7	21	0.749	0.871
	2	67.8	68.5	9.6	47.8	83.5	62.0	75.6	22	0.762	
	3	70.5	67.8	10.9	46.2	85.0	61.0	74.2	20	0.356	
	4	71.3	69.8	6.8	53.5	80.5	67.4	74.3	21	0.179	
2	1	72.8	72.4	7.2	56.5	83.3	68.5	79.0	21	0.632	0.543
	2	69.0	70.1	12.7	50.8	97.3	60.8	79.5	22	0.422	
	3	70.1	71.1	13.3	48.8	94.0	64.9	80.7	20	0.473	
	4	76.0	73.5	10.1	54.5	87.5	68.3	81.2	21	0.088	
3	1	79.5	78.1	9.6	59.5	100.0	71.5	81.8	21	0.402	0.609
	2	75.2	74.7	11.8	51.8	94.7	67.3	84.0	22	0.736	
	3	81.3	78.8	16.5	49.3	106.0	67.5	89.9	20	0.497	
	4	78.7	78.3	10.1	56.7	92.3	74.0	86.8	21	0.144	
4	1	74.0	75.0	9.2	58.0	90.5	71.8	79.8	21	0.578	0.558
	2	71.6	71.8	11.2	50.3	93.0	65.0	79.3	22	0.936	
	3	76.1	74.4	14.6	43.8	95.0	65.3	86.9	20	0.200	
	4	76.3	76.3	8.5	57.3	90.5	71.3	83.8	21	0.863	
5	1	75.5	76.7	12.1	59.0	102.3	69.3	85.0	21	0.632	0.508
	2	75.6	74.8	11.2	50.0	94.0	66.3	81.8	22	0.845	
	3	79.8	78.0	14.6	46.0	106.3	70.0	87.5	20	0.892	
	4	79.8	79.9	8.8	63.3	100.0	75.0	84.5	21	0.977	
6	1	75.8	75.8	9.9	62.0	93.5	66.7	83.7	21	0.238	0.646
	2	75.8	75.7	11.2	51.5	97.0	67.0	84.8	22	0.959	
	3	76.1	76.7	15.3	45.8	100.3	65.1	89.0	20	0.628	
	4	79.8	79.4	8.3	65.8	97.5	74.3	85.8	21	0.897	
7	1	76.0	78.5	9.5	61.8	93.3	72.8	88.0	21	0.245	0.919
	2	78.3	80.5	14.1	52.8	120.3	71.5	89.0	22	0.177	
	3	83.7	78.9	17.0	47.5	102.3	66.8	90.9	20	0.113	
	4	78.8	79.9	11.4	67.7	121.3	73.5	82.0	21	0.000*	
8	1	74.0	77.6	12.9	60.5	109.8	68.5	80.8	21	0.089	0.677
	2	79.8	80.6	15.1	45.8	109.3	71.0	91.5	22	0.734	
	3	83.0	79.3	18.0	44.3	107.3	65.6	91.3	20	0.461	
	4	75.8	77.9	9.6	66.0	101.5	71.5	80.8	21	0.029*	
9	1	75.8	80.3	16.5	58.5	123.0	67.5	91.5	21	0.082	0.922
	2	76.8	80.3	20.1	44.3	145.0	68.0	90.0	22	0.014*	
	3	81.0	78.0	16.4	42.5	105.5	68.7	90.0	20	0.554	
	4	72.0	76.2	9.3	64.8	93.8	69.5	83.3	21	0.025*	
10	1	75.8	75.7	10.2	54.8	104.5	71.0	79.0	21	0.143	0.692
	2	77.5	77.1	12.4	50.3	99.5	68.3	89.0	22	0.704	
	3	82.6	78.0	13.6	51.0	96.5	70.0	87.1	20	0.097	
	4	77.0	76.2	8.4	55.8	92.0	71.3	80.8	21	0.608	
11	1	82.3	84.7	13.0	63.8	113.0	76.5	93.0	21	0.637	0.840
	2	87.2	88.4	13.2	65.3	118.7	78.0	94.8	22	0.884	
	3	83.9	83.4	17.4	49.7	107.8	75.8	97.6	20	0.187	
	4	85.3	86.0	9.6	73.0	105.7	80.5	91.3	21	0.266	

Table 2a cont.

Summary Statistics and Tests for Time and Drug

After Data Replaced: Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
12	1	76.0	81.1	16.2	58.3	115.0	68.0	92.0	21	0.098	0.643
	2	85.9	85.2	14.8	56.7	108.8	72.8	94.0	22	0.570	
	3	82.4	82.0	17.8	51.7	118.5	73.5	91.4	20	0.636	
	4	81.5	82.3	8.4	63.5	94.0	77.7	89.0	21	0.224	
13	1	78.0	77.2	12.5	55.0	97.0	68.5	86.5	21	0.516	0.995
	2	78.5	78.3	15.3	47.0	109.0	69.0	85.8	22	0.937	
	3	77.5	77.2	17.2	45.0	109.5	67.5	86.3	20	0.920	
	4	77.0	78.9	12.3	66.0	113.0	73.5	82.0	21	0.000*	
14	1	73.0	72.8	9.2	54.0	90.5	65.5	78.0	21	0.815	0.642
	2	77.0	76.2	12.6	47.0	107.0	70.0	84.0	22	0.823	
	3	71.8	72.8	13.6	43.0	101.5	64.3	82.5	20	0.984	
	4	74.5	75.7	8.4	64.0	93.5	69.0	79.0	21	0.182	
15	1	70.0	72.1	11.9	51.5	100.5	66.0	75.0	21	0.038*	0.825
	2	67.8	73.1	14.4	48.5	102.5	64.0	82.0	22	0.125	
	3	68.3	69.6	10.7	51.3	89.0	62.3	75.5	20	0.691	
	4	71.0	73.1	11.2	54.5	106.5	67.0	75.5	21	0.016*	
16	1	70.0	69.4	8.4	54.0	89.5	63.0	75.0	21	0.901	0.827
	2	67.3	69.6	14.1	46.0	104.0	60.5	82.5	22	0.490	
	3	66.0	66.5	10.8	44.5	87.0	61.0	72.0	20	0.777	
	4	66.0	68.2	9.4	50.0	88.0	62.0	71.0	21	0.108	
17	1	69.5	69.3	7.4	55.5	83.0	63.0	75.0	21	0.946	0.848
	2	68.0	69.4	12.5	45.0	94.0	61.0	76.5	22	0.903	
	3	67.3	66.3	10.4	42.5	85.5	61.3	72.5	20	0.540	
	4	67.0	68.5	8.5	53.0	86.5	62.5	73.5	21	0.655	
18	1	68.0	68.5	8.1	54.0	82.0	62.5	77.0	21	0.506	0.427
	2	62.5	64.6	10.3	47.5	85.5	57.0	73.0	22	0.704	
	3	66.3	65.7	10.8	40.0	82.0	61.5	72.8	20	0.330	
	4	66.5	68.5	6.7	56.5	82.5	64.0	73.0	21	0.862	
19	1	67.0	66.8	7.1	49.5	78.0	63.5	72.0	21	0.645	0.850
	2	65.5	64.3	9.6	44.0	79.0	57.5	72.5	22	0.656	
	3	68.3	66.1	10.5	45.5	84.0	60.3	73.3	20	0.775	
	4	65.5	67.3	7.4	53.0	82.0	63.0	70.0	21	0.724	
20	1	64.5	66.0	8.6	54.0	85.0	61.0	71.0	21	0.390	0.784
	2	63.3	65.0	11.8	45.0	95.0	56.0	70.5	22	0.257	
	3	64.3	64.7	11.0	41.5	84.0	57.5	73.5	20	0.912	
	4	65.5	66.4	4.8	57.5	75.0	63.5	70.0	21	0.671	
21	1	66.0	68.6	8.9	55.5	94.0	62.0	75.0	21	0.082	0.269
	2	60.5	62.6	9.7	45.0	83.0	55.5	69.0	22	0.384	
	3	67.8	65.6	11.6	40.5	84.0	58.3	74.3	20	0.697	
	4	65.0	67.3	10.3	57.0	106.5	64.5	67.5	21	0.000*	
22	1	75.0	72.9	11.7	52.5	100.0	62.5	80.0	21	0.568	0.524
	2	69.8	72.3	15.6	43.5	103.5	60.0	82.5	22	0.573	
	3	70.8	69.6	13.1	45.0	88.0	59.3	81.3	20	0.301	
	4	74.0	75.7	11.6	61.0	102.5	67.0	83.0	21	0.101	
23	1	90.8	90.5	15.5	59.5	118.0	78.1	102.5	21	0.947	0.184
	2	81.8	89.5	25.7	50.3	173.0	74.3	101.3	22	0.006*	
	3	78.6	79.9	14.4	51.0	105.0	72.6	88.1	20	0.636	
	4	84.3	88.0	12.4	72.5	122.7	79.0	95.0	21	0.036*	
24	1	77.0	78.4	10.2	61.8	102.0	71.5	83.0	21	0.626	0.120
	2	72.7	74.1	10.0	54.5	94.0	69.0	77.8	22	0.299	
	3	74.0	72.8	12.6	47.0	104.7	67.3	80.5	20	0.510	
	4	78.5	80.5	12.5	60.5	105.7	76.8	88.3	21	0.167	

Table 2b

Summary Statistics and Tests for Time and Drug

After Data Replaced: Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	149.7	151.3	12.1	128.4	174.4	143.1	158.8	20	0.968	0.866
	2	146.8	148.7	11.1	128.5	177.6	143.2	154.1	21	0.385	
	3	147.2	152.2	13.7	129.9	179.6	144.8	160.3	20	0.029*	
	4	149.0	149.1	13.6	128.5	167.3	139.8	162.6	21	0.066	
1	1	153.5	153.6	13.9	127.3	178.0	143.8	162.5	21	0.910	0.022*
	2	150.8	151.4	12.7	122.0	170.0	144.8	163.8	22	0.278	
	3	155.5	155.0	19.0	99.4	184.0	147.3	166.3	20	0.110	
	4	143.0	143.3	11.6	125.0	168.5	137.8	149.3	21	0.808	
2	1	153.5	153.9	13.9	127.0	177.8	146.0	164.8	21	0.864	0.111
	2	149.1	152.5	12.2	129.5	172.3	143.8	162.6	22	0.416	
	3	147.3	150.1	16.6	107.5	183.3	140.8	163.0	20	0.607	
	4	145.5	142.9	14.0	111.3	166.2	132.5	152.0	21	0.727	
3	1	162.3	158.2	16.6	122.5	185.5	142.3	170.8	21	0.374	0.012*
	2	152.8	152.4	14.1	127.3	188.0	145.7	158.3	22	0.298	
	3	152.5	151.8	13.6	115.0	176.7	144.9	157.8	20	0.369	
	4	146.5	142.9	11.1	122.0	158.5	131.3	150.3	21	0.025*	
4	1	155.3	154.6	16.9	125.0	196.8	140.3	159.5	21	0.633	0.186
	2	149.1	151.3	15.1	130.3	178.8	137.8	160.3	22	0.089	
	3	148.8	148.0	17.5	96.3	177.0	141.4	155.1	20	0.058	
	4	142.0	142.1	15.2	112.5	166.8	138.0	151.5	21	0.426	
5	1	157.0	157.0	14.6	125.8	184.0	150.5	165.5	21	0.947	0.035*
	2	152.0	153.9	13.7	124.5	179.5	145.3	165.7	22	0.990	
	3	152.6	152.3	16.3	109.3	193.8	144.6	159.1	20	0.141	
	4	147.3	144.8	12.5	117.8	169.8	139.0	152.7	21	0.922	
6	1	154.0	156.0	17.3	119.5	198.5	144.8	163.3	21	0.149	0.006*
	2	150.7	150.9	12.3	124.5	174.0	140.8	157.3	22	0.856	
	3	147.4	147.8	20.0	108.0	186.3	134.6	157.6	20	0.903	
	4	138.5	139.3	13.3	116.0	169.0	132.0	146.5	21	0.752	
7	1	158.0	156.6	19.2	116.0	192.0	143.0	166.5	21	0.690	0.024*
	2	151.4	153.5	11.9	129.3	178.5	144.0	161.8	22	0.985	
	3	149.9	150.5	15.0	109.7	176.5	145.2	158.5	20	0.378	
	4	144.3	141.8	12.7	120.8	166.0	133.0	150.0	21	0.465	
8	1	149.0	153.3	16.6	118.8	184.3	142.0	164.0	21	0.483	0.042*
	2	147.7	154.1	16.7	118.8	187.0	143.3	168.3	22	0.214	
	3	146.8	147.1	17.1	100.3	173.3	139.9	158.9	20	0.201	
	4	139.8	142.0	15.4	118.0	178.0	131.5	152.3	21	0.502	
9	1	159.8	156.7	16.8	120.8	185.5	146.0	163.7	21	0.786	0.151
	2	148.4	150.2	15.4	123.3	182.0	137.8	163.7	22	0.902	
	3	154.1	152.4	17.6	112.8	186.8	139.5	162.6	20	0.972	
	4	144.8	144.7	14.9	116.0	169.5	135.0	154.7	21	0.815	
10	1	159.5	159.4	14.5	124.8	189.5	148.8	170.5	21	0.839	0.050
	2	150.3	151.7	13.6	127.8	178.0	140.7	160.8	22	0.449	
	3	154.8	155.5	20.8	100.3	193.0	145.3	168.1	20	0.498	
	4	148.3	146.5	13.1	125.8	173.5	134.3	155.3	21	0.317	
11	1	163.8	161.7	17.7	125.3	192.0	154.0	170.0	21	0.748	0.058
	2	150.8	153.9	18.7	115.3	184.0	145.3	169.8	22	0.343	
	3	153.3	154.1	17.2	116.3	191.8	145.1	162.2	20	0.959	
	4	148.5	146.5	15.1	121.7	168.8	133.3	158.0	21	0.219	
12	1	157.5	156.6	18.8	118.0	184.0	142.3	176.0	21	0.538	0.052
	2	150.6	153.0	16.0	122.0	187.5	142.0	162.7	22	0.884	
	3	150.4	149.7	17.0	111.0	181.5	144.6	158.2	20	0.358	
	4	145.3	142.5	11.6	124.0	165.7	133.0	150.5	21	0.264	

Table 2b cont.
Summary Statistics and Tests for Time and Drug
After Data Replaced: Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
13	1	150.5	151.3	16.6	115.5	177.5	142.5	163.5	21	0.715	0.117
	2	149.5	151.5	17.4	116.0	196.5	142.0	161.0	22	0.548	
	3	149.5	148.5	18.1	105.0	186.0	138.5	158.8	20	0.881	
	4	144.0	141.4	14.4	114.5	175.5	135.5	148.0	21	0.536	
14	1	151.5	152.1	12.4	129.0	180.0	146.0	159.0	21	0.890	0.084
	2	150.0	148.8	15.4	118.5	174.0	139.0	163.0	22	0.539	
	3	147.0	148.1	20.6	95.0	186.5	137.3	163.3	20	0.534	
	4	141.5	140.9	14.2	114.0	166.0	133.0	148.5	21	0.786	
15	1	145.0	145.8	18.5	108.5	181.0	136.0	156.5	21	0.935	0.163
	2	146.3	147.0	15.6	117.0	172.0	141.0	159.5	22	0.234	
	3	135.8	141.1	20.6	96.0	187.0	130.5	155.3	20	0.884	
	4	140.5	136.9	13.4	114.0	160.0	124.0	148.5	21	0.139	
16	1	136.5	138.1	17.6	115.0	192.0	127.0	144.0	21	0.006*	0.002*
	2	138.5	136.9	15.2	99.0	160.0	131.0	146.0	22	0.221	
	3	127.5	132.8	16.9	112.5	183.5	122.0	137.3	20	0.002*	
	4	122.5	123.5	11.2	102.5	148.5	115.5	132.5	21	0.662	
17	1	139.5	136.1	17.8	98.5	175.0	124.0	145.5	21	0.921	0.036*
	2	133.8	133.8	14.3	106.0	166.0	126.0	139.0	22	0.179	
	3	129.8	131.6	14.2	105.0	162.0	122.5	139.0	20	0.643	
	4	125.0	122.8	14.7	103.0	160.5	109.5	133.5	21	0.189	
18	1	133.5	136.0	18.3	108.0	179.0	122.0	146.5	21	0.574	0.039*
	2	132.8	131.1	13.8	107.0	154.0	119.5	140.0	22	0.492	
	3	128.8	132.4	20.8	102.0	193.5	118.3	142.8	20	0.063	
	4	115.5	120.2	15.6	91.0	144.5	110.0	136.5	21	0.167	
19	1	127.5	130.8	21.0	91.5	187.5	118.0	137.0	21	0.118	0.033*
	2	131.8	130.3	10.8	113.0	148.0	120.0	138.0	22	0.087	
	3	129.8	130.0	17.6	90.5	167.5	118.1	138.3	20	0.916	
	4	118.3	117.9	14.5	84.5	141.0	110.0	128.0	21	0.838	
20	1	128.5	130.7	19.9	97.0	176.0	115.0	139.0	21	0.282	0.335
	2	132.5	131.9	15.2	104.0	180.5	121.0	140.5	22	0.016*	
	3	131.0	131.6	17.3	103.0	166.0	116.3	144.0	20	0.840	
	4	123.5	122.9	14.7	83.0	147.0	114.0	133.0	21	0.379	
21	1	134.5	134.5	18.1	111.0	175.0	121.5	141.0	21	0.175	0.020*
	2	130.0	130.6	13.1	106.0	165.5	122.0	134.0	22	0.034*	
	3	133.0	133.1	17.6	99.0	166.5	122.8	142.3	20	0.651	
	4	118.5	119.9	14.6	96.0	146.5	111.0	129.0	21	0.464	
22	1	135.0	143.6	21.6	117.5	196.5	129.5	152.5	21	0.018*	0.491
	2	144.0	142.3	16.2	117.5	179.5	133.0	152.0	22	0.343	
	3	139.8	139.6	19.1	98.5	167.0	132.0	154.8	20	0.452	
	4	136.0	133.7	16.5	101.5	166.0	120.5	145.0	21	0.852	
23	1	157.4	158.6	19.9	129.0	203.0	148.5	167.5	21	0.388	0.007*
	2	153.8	150.1	14.3	120.0	177.0	143.3	158.5	22	0.242	
	3	151.0	152.5	22.9	91.0	183.3	142.0	172.7	20	0.235	
	4	139.7	140.1	13.8	112.7	174.0	129.8	150.0	21	0.719	
24	1	153.3	152.4	15.5	119.5	179.7	143.8	162.3	21	0.982	0.036*
	2	147.1	149.1	11.6	124.3	178.0	141.3	155.5	22	0.422	
	3	152.0	154.5	20.1	120.5	201.5	140.9	161.3	20	0.054	
	4	141.0	142.0	14.1	122.0	182.0	132.0	150.0	21	0.091	

Table 2c

Summary Statistics and Tests for Time and Drug After Data Replaced: Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	1	97.5	96.9	6.8	82.1	111.3	92.4	100.2	20	0.995	0.894
	2	96.4	95.0	5.9	82.2	103.9	92.8	99.4	21	0.128	
	3	94.8	96.1	6.9	83.9	109.8	91.6	101.2	20	0.663	
	4	95.1	95.6	8.7	81.8	113.0	89.5	99.0	21	0.425	
1	1	98.0	98.5	8.7	81.3	115.8	95.3	102.8	21	0.728	0.118
	2	99.4	99.2	9.0	81.3	115.4	94.0	105.6	22	0.964	
	3	100.8	98.7	10.6	67.6	114.0	94.2	105.5	20	0.045*	
	4	95.0	94.2	6.8	82.0	105.3	91.0	99.3	21	0.540	
2	1	100.5	98.2	10.0	82.0	115.3	90.0	106.8	21	0.536	0.164
	2	98.5	99.6	10.5	81.8	123.8	93.0	106.0	22	0.859	
	3	93.5	94.5	9.8	76.3	111.0	87.5	103.6	20	0.709	
	4	93.5	93.1	8.6	77.0	109.0	87.8	98.0	21	0.981	
3	1	104.5	103.0	10.6	80.8	115.3	96.8	112.8	21	0.061	0.020*
	2	102.0	100.8	11.3	74.7	121.3	90.8	110.2	22	0.658	
	3	94.3	95.9	10.3	79.0	113.0	87.4	105.0	20	0.323	
	4	90.5	94.0	9.8	80.0	115.0	87.0	99.3	21	0.305	
4	1	100.5	100.3	10.7	80.3	116.5	94.8	106.0	21	0.475	0.065
	2	101.3	99.4	11.2	75.8	123.0	91.8	107.8	22	0.992	
	3	93.6	92.2	10.8	68.3	108.3	86.4	101.1	20	0.525	
	4	97.6	93.2	10.9	69.3	110.5	86.5	100.0	21	0.200	
5	1	105.3	103.2	9.9	81.8	118.0	99.0	110.5	21	0.094	0.030*
	2	99.5	101.8	10.7	87.5	132.5	93.8	109.8	22	0.068	
	3	96.5	96.6	10.8	69.0	114.5	91.0	104.8	20	0.402	
	4	94.3	95.8	7.2	83.0	109.3	91.5	101.0	21	0.594	
6	1	93.0	94.8	9.7	74.0	112.8	90.8	103.3	21	0.497	0.016*
	2	93.5	94.6	10.0	80.0	119.0	86.0	101.0	22	0.091	
	3	85.9	87.4	9.0	67.0	103.3	82.6	94.8	20	0.641	
	4	88.3	87.8	8.2	71.3	106.8	82.0	91.7	21	0.695	
7	1	99.5	98.3	11.8	73.0	121.3	94.7	106.8	21	0.621	0.015*
	2	98.3	99.0	7.8	86.3	119.5	93.0	103.0	22	0.408	
	3	93.5	93.7	9.2	74.7	113.5	89.0	98.6	20	0.666	
	4	94.0	91.7	7.7	76.0	102.0	85.5	98.5	21	0.244	
8	1	100.5	100.2	9.4	77.8	113.5	95.0	106.0	21	0.513	0.003*
	2	102.5	102.6	11.8	82.3	133.7	98.0	108.0	22	0.227	
	3	93.6	93.7	9.4	75.0	112.8	86.7	98.1	20	0.969	
	4	91.0	92.8	7.8	81.5	109.8	88.3	97.3	21	0.099	
9	1	99.7	99.4	10.2	81.5	116.8	91.3	108.8	21	0.664	0.633
	2	97.5	97.5	9.6	79.3	114.8	91.3	105.3	22	0.821	
	3	95.4	95.9	11.1	75.3	114.3	88.9	101.5	20	0.587	
	4	95.3	96.2	11.6	79.0	125.5	90.0	101.0	21	0.446	
10	1	102.8	102.2	10.2	80.0	122.0	97.8	108.8	21	0.503	0.019*
	2	97.2	97.8	6.6	88.0	111.8	93.3	102.5	22	0.338	
	3	95.4	95.0	12.1	63.0	117.5	90.5	98.7	20	0.076	
	4	93.8	94.1	9.3	77.5	110.7	87.3	97.8	21	0.545	
11	1	108.0	104.6	13.0	76.3	124.0	99.0	114.0	21	0.496	0.031*
	2	102.1	103.5	13.4	86.5	140.0	93.3	109.0	22	0.045*	
	3	94.0	95.8	11.1	78.5	113.0	88.8	104.1	20	0.277	
	4	93.5	94.9	10.9	75.0	117.3	88.3	100.6	21	0.743	
12	1	104.3	97.5	14.3	60.3	117.0	92.3	106.5	21	0.030*	0.293
	2	96.5	96.2	9.9	78.3	117.0	90.7	102.7	22	0.299	
	3	91.7	93.1	9.4	78.3	108.0	85.8	100.4	20	0.312	
	4	93.5	93.7	9.5	74.8	114.0	90.0	98.0	21	0.676	

Table 2c cont.

Summary Statistics and Tests for Time and Drug
After Data Replaced: Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
13	1	98.0	96.2	11.9	66.0	120.5	88.0	101.0	21	0.267	0.279
	2	98.5	96.8	10.0	72.5	113.0	91.0	103.0	22	0.761	
	3	92.8	92.7	11.2	70.0	110.5	86.5	99.0	20	0.621	
	4	94.0	91.5	11.3	69.0	108.5	83.0	97.0	21	0.415	
14	1	94.8	95.2	9.8	77.0	110.5	88.5	104.0	21	0.538	0.474
	2	92.8	93.6	14.0	66.0	114.0	86.5	103.0	22	0.166	
	3	92.0	89.9	14.0	56.5	113.0	83.8	99.3	20	0.222	
	4	89.0	91.7	11.8	77.5	122.5	83.0	96.0	21	0.017*	
15	1	90.5	89.8	16.1	56.5	112.5	84.0	100.0	21	0.248	0.090
	2	95.8	95.6	15.1	69.0	121.5	79.5	107.0	22	0.602	
	3	85.5	83.8	13.3	51.0	106.0	78.5	92.0	20	0.197	
	4	85.0	86.9	12.1	64.5	112.5	80.0	91.5	21	0.810	
16	1	81.5	84.2	12.0	70.0	119.0	78.0	89.5	21	0.011*	0.008*
	2	82.5	85.4	12.0	63.0	107.5	78.0	98.0	22	0.691	
	3	75.0	77.3	10.5	58.0	97.5	70.3	85.0	20	0.695	
	4	74.0	75.3	9.4	57.0	95.5	70.5	79.0	21	0.626	
17	1	80.0	81.8	10.4	55.5	100.5	78.5	91.0	21	0.143	0.073
	2	80.8	81.4	10.0	66.0	104.5	74.0	89.5	22	0.752	
	3	82.3	80.8	11.5	58.5	98.0	72.8	89.0	20	0.680	
	4	71.5	72.8	13.3	49.5	99.0	66.0	81.5	21	0.928	
18	1	80.0	82.2	12.7	61.5	107.5	78.0	86.5	21	0.295	0.147
	2	81.0	81.8	10.3	62.5	100.0	74.5	89.5	22	0.521	
	3	80.3	78.9	12.1	62.0	101.5	68.8	87.3	20	0.405	
	4	70.0	74.1	13.5	54.5	97.5	65.5	86.0	21	0.060	
19	1	78.5	79.5	13.6	49.0	113.0	73.0	86.0	21	0.225	0.214
	2	80.8	81.1	9.5	66.0	97.5	74.0	88.0	22	0.213	
	3	77.0	77.4	10.9	51.0	94.5	69.0	85.3	20	0.659	
	4	73.0	73.5	11.7	48.5	95.5	68.0	82.0	21	0.998	
20	1	78.5	81.0	12.8	57.0	108.5	74.5	86.5	21	0.340	0.459
	2	82.0	81.8	7.2	70.5	103.5	77.5	84.0	22	0.025*	
	3	81.8	81.2	10.4	64.0	99.5	73.8	89.5	20	0.701	
	4	74.5	77.1	13.7	42.0	106.5	71.5	84.0	21	0.244	
21	1	82.5	82.8	9.1	70.0	108.0	78.0	87.0	21	0.111	0.020*
	2	82.3	82.0	7.8	69.0	102.5	78.0	86.0	22	0.480	
	3	82.5	81.4	11.1	58.5	99.0	72.3	87.8	20	0.612	
	4	72.5	74.2	11.5	56.0	99.0	67.5	76.5	21	0.071	
22	1	87.5	89.0	11.9	69.5	111.0	83.0	97.5	21	0.294	0.810
	2	89.5	90.8	10.7	72.5	108.5	83.0	96.5	22	0.539	
	3	90.0	87.6	13.4	62.5	107.0	76.8	100.0	20	0.461	
	4	88.0	87.1	13.2	65.0	110.0	77.0	98.0	21	0.653	
23	1	97.7	98.3	12.7	76.0	124.5	92.8	105.3	21	0.666	0.530
	2	100.3	98.2	10.4	66.0	115.3	92.0	104.3	22	0.032*	
	3	96.3	95.7	12.1	58.0	112.3	89.5	104.3	20	0.022*	
	4	93.0	94.4	10.2	74.0	111.9	89.0	100.0	21	0.878	
24	1	96.8	97.0	10.6	77.5	115.7	92.3	104.5	21	0.499	0.128
	2	96.4	97.2	7.1	86.7	113.3	92.3	101.5	22	0.472	
	3	96.4	97.3	8.5	81.5	117.0	92.3	102.8	20	0.902	
	4	92.0	92.3	8.7	79.0	113.8	85.0	96.0	21	0.151	

Table 2d
Summary Statistics and Tests by Time and Therapy
After Data Replaced: Dietary Response

TIME	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
0	Group1	0.9	1.0	0.1	0.8	1.1	0.9	1.0	8	0.835	0.495
	Group2	1.0	1.0	0.1	0.8	1.1	1.0	1.1	7	0.359	
	Group3	1.0	1.0	0.1	0.9	1.1	1.0	1.1	7	0.749	
1	Group1	0.9	0.9	0.1	0.7	1.1	0.8	1.0	8	0.952	0.090
	Group2	0.8	0.8	0.1	0.6	0.9	0.7	0.9	7	0.975	
	Group3	0.8	0.8	0.1	0.6	0.9	0.7	0.8	7	0.562	
2	Group1	0.8	0.8	0.1	0.6	1.0	0.8	1.0	8	0.350	0.013*
	Group2	0.7	0.7	0.1	0.6	0.7	0.6	0.7	7	0.412	
	Group3	0.7	0.7	0.1	0.5	0.8	0.6	0.7	7	0.835	
3	Group1	0.8	0.8	0.1	0.7	0.9	0.7	0.8	8	0.795	0.004*
	Group2	0.7	0.6	0.1	0.5	0.7	0.5	0.7	7	0.109	
	Group3	0.6	0.6	0.1	0.5	0.6	0.5	0.6	7	0.028*	
4	Group1	0.8	0.8	0.1	0.7	0.9	0.8	0.9	8	0.231	0.011*
	Group2	0.6	0.7	0.2	0.5	0.9	0.5	0.8	7	0.665	
	Group3	0.6	0.6	0.1	0.5	0.8	0.5	0.6	7	0.557	
5	Group1	0.9	0.9	0.1	0.7	1.1	0.9	1.0	8	0.866	<0.001*
	Group2	0.8	0.8	0.1	0.7	0.9	0.8	0.9	7	0.856	
	Group3	0.5	0.5	0.1	0.4	0.7	0.4	0.6	7	0.782	
6	Group1	1.0	1.0	0.1	0.8	1.1	0.8	1.1	8	0.170	<0.001*
	Group2	0.7	0.7	0.1	0.6	0.9	0.6	0.8	7	0.912	
	Group3	0.5	0.5	0.0	0.4	0.5	0.5	0.5	7	0.023*	
7	Group1	1.0	1.0	0.1	0.9	1.1	0.9	1.1	8	0.277	<0.001*
	Group2	0.9	0.8	0.1	0.7	0.9	0.7	0.9	7	0.261	
	Group3	0.5	0.5	0.0	0.5	0.5	0.5	0.5	7	0.127	
8	Group1	1.0	1.0	0.1	0.8	1.2	0.9	1.1	8	0.844	<0.001*
	Group2	0.8	0.8	0.1	0.7	1.0	0.8	0.9	7	0.961	
	Group3	0.5	0.5	0.1	0.4	0.6	0.5	0.6	7	0.777	
9	Group1	1.0	1.0	0.1	0.8	1.1	0.9	1.0	8	0.074	<0.001*
	Group2	0.8	0.8	0.1	0.7	0.9	0.7	0.9	7	0.334	
	Group3	0.5	0.5	0.0	0.5	0.5	0.5	0.5	7	0.755	

Table 3a
Summary Statistics and Tests for Time and Drug
After Data Replaced: Average 3 Hrs Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	75.0	73.7	7.1	59.8	84.8	68.8	79.8	21	0.656	0.704
	2	70.4	71.1	10.6	50.5	90.3	64.7	76.9	22	0.888	
	3	74.0	72.6	11.8	48.6	93.7	66.9	80.4	20	0.280	
	4	76.0	73.9	8.3	54.9	83.4	72.9	79.4	21	0.008*	
2	1	74.8	75.9	9.6	59.7	91.5	68.9	82.7	21	0.507	0.503
	2	73.8	74.1	10.5	50.6	94.7	67.6	83.1	22	0.989	
	3	79.1	76.3	14.1	47.3	99.1	69.7	87.4	20	0.189	
	4	77.6	78.5	7.8	62.7	91.1	74.3	85.1	21	0.820	
3	1	75.8	78.8	11.5	60.3	101.6	69.3	89.4	21	0.475	0.821
	2	78.3	80.5	15.5	47.6	124.0	71.5	85.3	22	0.101	
	3	82.4	78.7	15.9	44.8	104.2	69.4	87.6	20	0.210	
	4	76.7	78.0	9.3	67.5	102.6	70.9	80.7	21	0.011*	
4	1	76.8	80.5	12.0	60.8	108.2	72.3	89.2	21	0.423	0.743
	2	84.1	83.6	11.8	57.4	102.8	74.2	94.6	22	0.787	
	3	83.2	81.1	15.4	51.9	105.8	75.2	90.0	20	0.232	
	4	80.4	81.5	6.5	69.7	95.2	78.2	85.8	21	0.794	
5	1	73.7	74.0	10.3	53.5	94.8	66.2	80.5	21	0.852	0.902
	2	75.3	75.8	13.4	47.5	105.7	67.3	84.4	22	0.992	
	3	73.1	73.2	12.7	47.9	100.0	66.4	80.3	20	0.944	
	4	75.6	75.9	8.4	63.5	94.0	69.8	79.7	21	0.184	
6	1	68.8	69.1	7.0	54.5	84.8	64.7	74.7	21	0.871	0.801
	2	65.2	67.9	11.6	46.2	88.8	60.2	78.0	22	0.330	
	3	67.3	66.2	10.4	42.3	84.3	60.8	72.0	20	0.640	
	4	66.3	68.4	7.6	53.2	84.8	63.8	73.2	21	0.598	
7	1	65.0	67.1	7.6	55.8	85.7	62.3	73.2	21	0.397	0.581
	2	63.1	63.9	9.7	44.7	82.7	57.0	72.2	22	0.576	
	3	67.6	65.4	10.3	43.3	82.2	58.9	72.3	20	0.735	
	4	65.0	67.0	6.5	58.5	85.7	63.8	68.7	21	0.034*	
8	1	80.5	80.6	10.7	61.2	103.3	73.3	87.2	21	0.912	0.169
	2	75.9	78.6	14.1	49.4	102.4	69.6	90.0	22	0.352	
	3	73.1	74.1	12.2	47.7	93.3	65.9	83.0	20	0.820	
	4	79.1	81.4	7.8	71.5	99.3	75.6	84.8	21	0.049*	

Table 3b
Summary Statistics and Tests for Time and Drug
After Data Replaced: Average 3 Hrs Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	156.3	155.2	13.9	125.6	180.4	147.5	163.7	21	0.841	0.024*
	2	151.6	152.1	11.9	126.3	175.1	144.3	162.3	22	0.933	
	3	151.9	152.3	15.7	107.3	179.6	145.8	162.9	20	0.160	
	4	146.2	143.1	11.4	120.8	161.2	133.9	151.9	21	0.365	
2	1	155.5	155.9	15.5	123.4	191.9	147.4	161.9	21	0.753	0.021*
	2	150.9	152.0	12.5	126.4	175.4	142.4	160.9	22	0.758	
	3	149.0	149.4	17.3	104.5	185.7	141.4	156.5	20	0.569	
	4	142.4	142.1	12.3	120.5	168.5	135.1	149.5	21	0.716	
3	1	156.2	155.5	16.7	118.5	184.9	144.3	163.8	21	0.651	0.044*
	2	151.5	152.6	12.0	126.3	178.6	144.4	159.8	22	0.832	
	3	148.8	150.0	15.9	107.6	178.3	144.0	157.3	20	0.320	
	4	143.9	142.8	13.1	118.3	168.8	133.4	150.4	21	0.846	
4	1	160.8	159.2	16.1	122.7	187.7	146.9	167.5	21	0.916	0.027*
	2	149.8	152.8	13.9	130.3	177.1	142.7	162.5	22	0.238	
	3	153.4	153.1	17.4	109.2	188.1	143.4	163.2	20	0.825	
	4	148.9	145.2	11.2	127.0	162.0	136.2	151.9	21	0.298	
5	1	153.2	149.7	13.8	119.3	177.2	143.7	155.7	21	0.300	0.061
	2	151.7	149.1	14.9	117.3	176.7	141.5	154.0	22	0.419	
	3	147.8	145.9	18.3	98.7	186.5	134.2	154.3	20	0.554	
	4	138.2	139.7	12.2	120.3	163.8	130.3	146.2	21	0.735	
6	1	136.2	136.7	16.6	108.2	176.2	128.5	141.0	21	0.187	0.008*
	2	133.8	133.9	12.6	108.5	156.3	126.8	144.2	22	0.904	
	3	129.3	132.3	16.1	111.8	179.7	122.3	137.5	20	0.018*	
	4	120.9	122.1	12.2	103.3	150.5	112.8	131.7	21	0.262	
7	1	128.8	132.0	18.7	99.8	178.3	120.2	137.5	21	0.094	0.068
	2	132.8	130.9	11.4	110.0	162.2	121.0	136.3	22	0.205	
	3	132.3	131.6	15.7	109.2	166.7	116.9	140.8	20	0.529	
	4	118.5	120.3	13.7	87.8	142.7	112.8	129.7	21	0.716	
8	1	152.8	151.5	16.3	126.2	186.8	141.8	157.4	21	0.289	0.028*
	2	148.0	147.1	11.8	120.6	170.8	141.8	155.3	22	0.970	
	3	146.8	148.9	19.0	105.5	182.5	137.3	158.8	20	0.840	
	4	140.3	138.6	12.7	117.6	174.0	129.4	145.6	21	0.128	

Table 3c
Summary Statistics and Tests for Time and Drug
After Data Replaced: Average 3 Hrs Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	101.4	99.9	8.7	81.7	115.2	95.1	105.7	21	0.682	0.084
	2	97.9	99.8	9.4	81.4	117.8	94.1	107.6	22	0.812	
	3	96.8	96.4	9.3	74.3	109.3	90.3	103.8	20	0.570	
	4	96.1	93.8	7.3	81.4	108.1	87.8	99.5	21	0.157	
2	1	99.7	99.4	9.3	78.7	115.0	97.3	104.3	21	0.233	0.012*
	2	98.0	98.6	10.0	81.1	124.8	91.3	105.4	22	0.587	
	3	90.5	92.1	9.3	68.1	108.0	88.9	99.7	20	0.341	
	4	93.4	92.2	7.7	75.6	107.0	88.8	97.5	21	0.862	
3	1	100.4	99.3	9.3	78.1	116.8	93.7	104.7	21	0.575	0.025*
	2	101.0	99.7	6.7	85.3	109.1	97.7	105.1	22	0.053	
	3	95.5	94.4	8.6	75.7	108.2	88.1	100.5	20	0.847	
	4	92.5	93.6	8.3	78.8	111.0	88.6	99.6	21	0.870	
4	1	105.3	101.4	10.9	72.2	114.3	97.7	108.8	21	0.011*	0.009*
	2	97.6	99.2	8.2	85.9	122.9	93.6	105.0	22	0.091	
	3	94.9	94.7	9.5	74.4	111.8	89.1	101.6	20	0.977	
	4	92.8	94.2	8.1	82.1	111.0	88.8	98.0	21	0.329	
5	1	94.3	93.8	9.5	75.7	107.2	92.0	101.2	21	0.076	0.103
	2	97.7	95.3	11.2	69.2	114.7	88.3	102.3	22	0.695	
	3	88.3	88.8	11.5	59.2	109.8	84.0	96.3	20	0.544	
	4	88.7	90.0	10.3	76.0	112.0	84.5	92.7	21	0.059	
6	1	82.5	82.7	10.1	62.5	108.0	76.8	86.2	21	0.094	0.024*
	2	81.8	82.9	8.8	68.5	99.3	77.7	90.5	22	0.407	
	3	79.8	79.0	9.7	64.2	96.2	71.3	86.2	20	0.486	
	4	73.2	74.1	10.4	58.0	94.8	68.7	82.5	21	0.739	
7	1	79.5	81.1	10.9	58.7	109.8	74.7	83.5	21	0.025*	0.057
	2	81.0	81.6	6.8	71.8	96.5	76.3	85.3	22	0.191	
	3	80.9	80.0	8.5	66.5	94.7	71.3	85.7	20	0.431	
	4	74.3	75.0	11.5	48.8	97.5	70.2	77.7	21	0.195	
8	1	95.5	94.8	8.7	75.8	108.3	89.2	99.8	21	0.738	0.263
	2	97.0	95.4	7.1	75.7	108.9	90.1	98.5	22	0.077	
	3	92.6	93.5	9.7	67.3	110.1	89.1	101.9	20	0.352	
	4	90.8	91.3	8.7	75.2	111.9	85.8	97.5	21	0.931	

Table 3d
Summary Statistics and Tests by Time and Therapy
After Data Replaced: Average 3 Hrs Dietary Response

TIME	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	group1	0.8	0.8	0.1	0.7	1.0	0.8	0.9	8	0.174	0.003*
	group2	0.7	0.7	0.1	0.6	0.8	0.7	0.8	7	0.420	
	group3	0.7	0.7	0.1	0.6	0.8	0.6	0.7	7	0.707	
2	group1	0.9	0.9	0.1	0.7	1.0	0.9	1.0	8	0.070	<0.001*
	group2	0.7	0.7	0.1	0.6	0.9	0.7	0.8	7	0.902	
	group3	0.5	0.5	0.1	0.5	0.6	0.5	0.6	7	0.685	
3	group1	1.0	1.0	0.1	0.9	1.1	0.9	1.0	8	0.178	<0.001*
	group2	0.8	0.8	0.1	0.7	0.9	0.8	0.9	7	0.407	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.5	7	0.231	

Table 4a

Summary Statistics and Tests for Time and Drug

After Data Replaced: Average 2 Hrs Heart Rate

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	73.1	71.5	7.6	57.3	84.8	67.5	76.0	21	0.806	0.722
	2	69.3	69.3	10.9	49.9	90.1	62.4	77.1	22	0.793	
	3	70.4	69.4	11.7	48.1	89.5	63.9	79.2	20	0.648	
	4	72.8	71.7	8.2	54.0	81.7	65.7	77.8	21	0.038*	
2	1	77.1	76.6	8.6	58.8	92.6	71.6	81.4	21	0.937	0.491
	2	73.1	73.3	11.0	51.0	91.4	67.5	81.5	22	0.749	
	3	81.3	76.6	14.8	46.7	94.5	67.4	88.3	20	0.033*	
	4	78.1	77.3	8.8	57.0	89.5	71.4	84.5	21	0.461	
3	1	75.6	76.3	10.4	60.5	93.0	68.3	85.7	21	0.214	0.526
	2	75.1	75.2	10.7	50.8	95.5	68.8	84.6	22	0.958	
	3	77.7	77.3	14.3	49.0	101.1	70.6	89.1	20	0.280	
	4	80.1	79.6	8.0	65.4	93.6	74.2	86.5	21	0.850	
4	1	76.3	78.1	10.7	61.1	101.5	70.3	84.4	21	0.577	0.729
	2	79.0	80.6	13.7	49.3	113.5	73.0	86.5	22	0.309	
	3	83.3	79.1	16.1	45.9	103.5	68.0	90.1	20	0.117	
	4	77.0	78.9	9.8	68.3	108.7	72.1	81.6	21	0.003*	
5	1	75.8	78.0	11.7	59.4	103.1	69.6	86.8	21	0.462	0.810
	2	77.6	78.7	15.0	47.3	117.7	67.9	88.1	22	0.366	
	3	81.9	78.0	14.4	46.8	101.0	69.7	87.4	20	0.219	
	4	74.5	76.2	8.0	63.9	92.2	70.0	82.3	21	0.464	
6	1	79.4	82.9	13.8	61.0	110.0	72.4	91.6	21	0.344	0.577
	2	88.0	86.8	12.9	61.0	106.0	74.7	97.3	22	0.496	
	3	81.9	82.7	17.0	52.3	110.6	76.5	92.1	20	0.257	
	4	83.4	84.1	7.0	68.9	97.5	80.8	86.2	21	0.311	
7	1	75.8	75.0	10.5	54.5	92.0	66.3	79.8	21	0.704	0.926
	2	78.6	77.2	13.7	47.0	107.3	68.8	83.8	22	0.975	
	3	73.5	75.0	15.0	46.3	105.5	66.0	86.8	20	0.940	
	4	75.0	77.3	9.0	65.8	103.3	71.5	80.5	21	0.018*	
8	1	68.8	70.7	9.4	52.8	95.0	66.0	73.5	21	0.170	0.896
	2	67.0	71.4	13.8	47.3	103.3	62.8	81.8	22	0.422	
	3	67.3	68.0	10.0	48.5	88.0	63.4	74.9	20	0.830	
	4	69.0	70.6	9.5	52.3	97.3	64.8	74.5	21	0.072	
9	1	68.0	68.9	7.3	54.8	82.5	64.5	75.3	21	0.916	0.776
	2	65.0	67.0	11.0	46.3	89.8	60.0	75.5	22	0.663	
	3	66.6	66.0	10.4	41.3	83.0	60.8	73.3	20	0.426	
	4	67.5	68.5	7.3	54.8	83.3	63.3	74.0	21	0.901	
10	1	65.8	66.4	7.6	52.3	81.5	61.3	71.5	21	0.992	0.824
	2	63.3	64.6	10.1	44.5	85.0	56.8	71.5	22	0.931	
	3	66.1	65.4	10.1	44.8	82.0	59.1	72.9	20	0.663	
	4	65.8	66.9	5.6	57.8	76.0	63.5	69.3	21	0.096	
11	1	70.0	70.7	9.0	58.3	88.5	62.5	77.5	21	0.219	0.597
	2	65.8	67.5	11.8	44.3	88.0	58.8	75.8	22	0.480	
	3	71.3	67.6	11.4	45.5	83.0	59.4	76.4	20	0.170	
	4	70.0	71.5	9.5	59.8	104.5	64.3	75.0	21	0.000*	
12	1	82.9	84.4	12.6	61.5	110.0	76.1	92.8	21	0.974	0.126
	2	75.9	81.8	16.0	52.4	124.4	73.4	93.1	22	0.103	
	3	76.4	76.3	12.6	49.0	102.5	68.4	83.8	20	0.993	
	4	80.7	84.3	10.7	69.5	112.5	78.4	89.7	21	0.024*	

Table 4b

Summary Statistics and Tests for Time and Drug

After Data Replaced: Average 2 Hrs Systolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	155.9	153.8	13.4	127.1	177.9	144.6	160.1	21	0.953	0.039*
	2	151.3	151.9	11.7	125.8	171.1	144.1	162.9	22	0.647	
	3	153.2	152.5	17.3	103.5	183.6	143.0	165.2	20	0.247	
	4	146.4	143.1	12.2	118.4	164.9	135.1	151.3	21	0.746	
2	1	159.9	156.4	16.1	123.8	191.1	146.0	164.4	21	0.873	0.030*
	2	148.3	151.8	13.8	128.8	182.4	141.8	158.9	22	0.632	
	3	149.9	149.9	15.2	105.6	174.3	145.9	157.4	20	0.061	
	4	145.5	142.5	12.4	117.3	162.6	136.0	152.2	21	0.044*	
3	1	156.0	156.5	15.2	122.6	189.5	147.8	163.1	21	0.743	0.011*
	2	150.6	152.4	12.3	124.5	174.8	144.3	161.6	22	0.714	
	3	150.2	150.1	17.8	108.6	190.0	138.3	158.0	20	0.843	
	4	143.5	142.1	12.1	120.9	169.4	131.1	148.1	21	0.688	
4	1	153.3	155.0	17.4	117.4	186.1	143.0	163.8	21	0.593	0.024*
	2	153.0	153.8	12.4	124.0	177.0	145.1	162.9	22	0.915	
	3	147.4	148.8	15.6	105.0	174.0	143.1	156.8	20	0.122	
	4	143.2	141.9	13.1	119.4	172.0	132.5	147.1	21	0.371	
5	1	154.5	158.0	14.9	122.8	187.0	148.5	166.3	21	0.850	0.055
	2	150.0	150.9	13.9	131.7	180.0	140.3	162.9	22	0.372	
	3	153.5	153.9	18.8	106.5	188.1	142.4	164.9	20	0.536	
	4	147.8	145.6	13.2	123.8	164.4	132.7	158.1	21	0.217	
6	1	161.1	159.2	17.4	121.6	186.8	147.0	166.0	21	0.584	0.034*
	2	154.8	153.4	15.7	130.3	181.5	140.6	164.5	22	0.369	
	3	151.4	151.9	16.3	113.7	185.6	142.0	161.6	20	0.985	
	4	145.8	144.5	12.1	124.7	164.2	134.3	154.3	21	0.379	
7	1	153.8	151.7	13.7	122.8	177.5	143.3	159.8	21	0.988	0.075
	2	150.6	150.1	15.5	117.3	185.3	141.8	160.5	22	0.870	
	3	150.0	148.3	18.3	100.0	186.3	136.5	158.4	20	0.491	
	4	139.5	141.1	13.4	118.3	170.8	133.3	148.3	21	0.882	
8	1	141.3	141.9	14.6	111.8	173.5	137.3	148.3	21	0.570	0.008*
	2	143.1	141.9	14.8	109.5	164.0	138.3	154.0	22	0.075	
	3	134.4	137.0	17.4	110.8	185.3	126.9	145.4	20	0.149	
	4	133.0	130.2	11.2	112.9	154.3	120.3	137.8	21	0.403	
9	1	135.0	136.0	17.1	104.8	172.8	124.5	144.0	21	0.790	0.034*
	2	131.5	132.5	13.4	107.8	160.0	124.8	139.3	22	0.421	
	3	129.6	132.0	16.5	108.5	177.8	120.5	140.8	20	0.173	
	4	122.0	121.5	14.1	98.5	151.5	110.5	134.0	21	0.222	
10	1	127.0	130.7	19.7	94.3	180.0	120.5	136.8	21	0.100	0.083
	2	132.4	131.1	11.7	112.0	164.3	120.5	138.3	22	0.096	
	3	133.0	130.8	16.5	105.5	166.8	116.5	140.4	20	0.453	
	4	118.5	120.4	14.1	83.8	142.5	113.3	130.3	21	0.355	
11	1	134.5	139.0	18.0	116.8	173.0	125.0	150.3	21	0.048*	0.103
	2	136.5	136.4	12.8	115.3	168.8	126.8	143.3	22	0.680	
	3	134.1	136.3	17.3	98.8	165.0	126.6	149.8	20	0.781	
	4	123.3	126.8	14.1	104.8	149.0	117.5	136.3	21	0.205	
12	1	154.9	155.5	16.9	124.3	191.3	146.6	162.6	21	0.896	0.007*
	2	150.1	149.6	12.2	122.2	177.5	143.8	156.0	22	0.985	
	3	155.9	153.5	20.4	105.8	192.1	141.3	162.8	20	0.684	
	4	138.0	141.0	12.9	121.6	178.0	131.4	147.8	21	0.077	

Table 4c
Summary Statistics and Tests for Time and Drug
After Data Replaced: Average 2 Hrs Diastolic Blood Pressure

TIME	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
1	1	98.9	98.4	8.9	82.1	115.3	94.0	104.6	21	0.777	0.206
	2	97.6	99.4	9.3	82.3	119.6	94.1	104.8	22	0.951	
	3	97.2	96.6	9.7	71.9	112.5	89.4	104.8	20	0.582	
	4	95.8	93.6	7.1	80.5	106.2	89.1	98.4	21	0.250	
2	1	102.3	101.6	9.9	80.5	115.3	97.3	109.6	21	0.114	0.021*
	2	101.7	100.1	10.6	75.2	118.7	90.8	106.4	22	0.868	
	3	92.1	94.1	9.8	73.6	110.6	89.0	102.4	20	0.842	
	4	94.0	93.6	9.0	76.3	105.1	86.6	101.0	21	0.172	
3	1	99.8	99.0	9.2	77.9	114.8	95.8	103.9	21	0.241	0.011*
	2	95.6	98.2	10.0	83.8	125.8	90.5	103.8	22	0.092	
	3	90.5	92.0	9.5	68.0	107.9	87.2	99.1	20	0.358	
	4	92.7	91.8	7.0	78.8	108.0	85.4	96.0	21	0.798	
4	1	100.8	99.3	10.0	76.4	117.4	95.0	104.3	21	0.423	0.003*
	2	101.7	100.8	8.4	86.0	118.2	95.4	104.8	22	0.477	
	3	93.3	93.7	8.7	74.8	112.2	88.8	98.6	20	0.981	
	4	91.1	92.2	7.2	78.8	104.1	87.3	96.4	21	0.587	
5	1	99.8	100.8	9.5	81.9	119.4	96.3	107.7	21	0.933	0.188
	2	97.3	97.6	7.1	86.5	110.4	92.8	104.4	22	0.517	
	3	97.5	95.5	10.6	70.3	115.5	89.6	101.2	20	0.472	
	4	92.0	95.1	9.8	80.3	116.1	88.1	101.7	21	0.660	
6	1	106.2	101.0	12.4	68.3	115.5	95.7	109.6	21	0.020*	0.044*
	2	98.9	99.8	10.6	83.6	128.5	92.0	104.0	22	0.193	
	3	92.1	94.5	9.4	79.8	110.3	88.3	102.1	20	0.421	
	4	93.8	94.3	8.9	82.3	111.3	87.0	97.1	21	0.174	
7	1	97.0	95.7	9.0	72.8	113.8	93.8	100.3	21	0.403	0.278
	2	97.6	95.2	10.8	69.3	113.5	87.0	100.5	22	0.700	
	3	90.8	91.3	11.7	63.3	111.8	87.1	99.3	20	0.752	
	4	89.3	91.6	10.5	75.3	111.8	84.8	94.8	21	0.224	
8	1	87.5	87.0	11.6	63.5	104.8	82.5	96.0	21	0.283	0.014*
	2	88.8	90.5	12.6	66.0	113.5	82.0	99.8	22	0.952	
	3	81.0	80.5	10.2	62.8	96.0	75.0	88.5	20	0.439	
	4	82.0	81.1	9.1	65.0	100.5	74.8	85.0	21	0.334	
9	1	80.5	82.0	10.5	58.5	102.8	79.3	86.0	21	0.326	0.077
	2	81.1	81.6	9.2	64.5	102.3	74.0	85.3	22	0.625	
	3	80.5	79.9	10.8	61.3	95.5	71.9	89.9	20	0.321	
	4	71.8	73.5	12.0	54.8	97.0	67.0	81.5	21	0.477	
10	1	77.8	80.2	12.6	53.0	110.8	75.0	85.0	21	0.090	0.229
	2	79.8	81.5	7.4	68.3	98.5	77.5	84.5	22	0.371	
	3	78.9	79.3	9.0	65.3	92.5	70.9	88.3	20	0.155	
	4	75.3	75.3	12.4	45.3	101.0	69.8	81.5	21	0.798	
11	1	86.5	85.9	8.6	73.8	103.0	79.0	91.0	21	0.471	0.217
	2	85.6	86.4	7.1	76.0	104.5	80.5	91.0	22	0.225	
	3	84.8	84.5	10.7	63.0	103.0	77.3	93.4	20	0.674	
	4	80.0	80.6	10.8	64.8	100.3	71.6	88.8	21	0.217	
12	1	97.2	97.7	10.8	78.4	120.1	92.3	103.3	21	0.785	0.205
	2	99.0	97.7	7.9	77.0	111.1	93.1	101.7	22	0.564	
	3	94.4	96.5	9.3	69.8	114.6	91.8	102.1	20	0.072	
	4	92.0	93.4	8.6	78.0	112.8	91.0	97.0	21	0.277	

Table 5a
Summary Statistics and Tests for Summary Measures and Drug: Original Data Set: Heart Rate

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	1.4	3.9	-2.9	12.1	-1.0	2.7	20	0.002*	0.161
	2	2.3	1.2	4.8	-12.0	9.5	-0.6	3.7	21	0.011*	
	3	1.3	1.2	4.5	-10.2	11.2	-0.2	2.9	22	0.475	
	4	3.7	3.5	4.6	-2.9	17.8	1.3	5.8	21	0.013*	
MEAN	1	72.7	75.0	8.0	59.2	90.2	70.2	82.1	21	0.528	0.985
	2	74.1	74.4	10.1	49.2	91.4	67.6	83.2	22	0.486	
	3	77.8	74.0	11.9	48.4	91.9	67.5	81.4	22	0.204	
	4	75.4	75.6	5.8	64.8	88.1	71.8	78.9	21	0.680	
MEDIAN	1	72.5	73.8	8.2	58.8	90.0	67.3	81.1	21	0.809	0.927
	2	72.3	72.9	9.7	48.1	88.4	66.4	78.3	22	0.421	
	3	75.8	73.2	12.2	48.3	90.1	65.6	83.0	22	0.222	
	4	75.3	75.0	6.1	64.4	89.0	70.8	77.4	21	0.504	
MIN	1	61.0	61.6	7.2	49.5	76.0	57.0	67.5	21	0.799	0.608
	2	58.3	59.2	8.7	43.5	79.0	52.0	66.0	22	0.789	
	3	61.0	59.9	9.3	40.0	77.3	54.0	65.5	22	0.863	
	4	62.0	61.7	5.2	50.0	71.5	58.0	64.0	21	0.801	
MAX	1	98.3	97.8	14.3	71.0	123.0	86.0	106.7	21	0.656	0.739
	2	100.6	101.9	21.3	65.3	173.0	88.3	109.3	22	0.006*	
	3	100.4	94.4	16.0	54.5	118.5	85.6	105.0	22	0.186	
	4	94.8	97.5	12.1	78.5	122.7	89.8	105.7	21	0.400	
Q1	1	68.0	68.4	6.9	55.3	82.6	63.3	74.0	21	0.661	0.904
	2	66.7	66.8	9.6	45.4	84.4	59.8	74.6	22	0.912	
	3	69.4	67.2	10.6	44.4	84.5	58.5	73.5	22	0.353	
	4	66.8	68.4	6.2	55.5	80.1	64.5	72.8	21	0.429	
Q3	1	78.3	80.3	10.0	61.9	101.7	74.7	87.5	21	0.721	0.987
	2	80.9	80.9	12.2	51.6	99.3	72.2	91.5	22	0.428	
	3	82.0	79.7	14.0	50.6	99.8	69.8	88.9	22	0.268	
	4	80.9	81.0	6.3	68.6	94.0	76.6	84.5	21	0.753	

Table 5b
Summary Statistics and Tests for Summary Measures and Drug Original Data Set: Systolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-1.9	-3.3	5.1	-14.8	2.9	-6.8	0.7	20	0.163	<0.001*
	2	-3.6	-2.7	6.8	-11.4	19.9	-6.9	-0.4	21	0.003*	
	3	-6.0	-6.9	6.9	-21.8	10.0	-11.8	-3.6	22	0.376	
	4	-9.1	-12.4	9.1	-32.2	2.7	-17.4	-6.5	21	0.259	
MEAN	1	150.9	149.5	14.5	121.7	179.8	138.2	156.2	21	0.967	0.015*
	2	146.5	146.3	10.8	122.3	170.8	139.7	154.0	22	0.996	
	3	143.6	145.4	14.3	108.2	175.9	137.1	153.7	22	0.531	
	4	138.0	136.7	10.5	119.5	151.4	131.3	143.8	21	0.171	
MEDIAN	1	150.5	151.8	14.3	121.6	177.9	141.1	159.4	21	0.770	0.015*
	2	146.4	147.2	11.7	121.5	173.9	140.9	152.5	22	0.975	
	3	147.6	147.6	14.5	108.6	175.3	139.9	154.5	22	0.329	
	4	139.6	138.3	10.6	119.5	157.1	131.3	146.8	21	0.358	
MIN	1	120.5	122.3	14.9	91.5	166.5	115.0	129.0	21	0.094	0.022*
	2	121.8	121.8	11.1	99.0	148.0	114.0	129.5	22	0.766	
	3	122.0	121.1	15.3	90.5	162.0	112.5	128.7	22	0.166	
	4	110.5	111.1	12.2	83.0	132.0	105.0	120.5	21	0.900	
MAX	1	170.8	172.0	18.4	130.0	203.0	165.5	183.0	21	0.473	0.065
	2	171.5	170.0	13.8	139.0	196.5	160.3	178.5	22	0.936	
	3	166.7	166.5	17.4	133.0	201.5	154.8	176.0	22	0.727	
	4	161.5	159.2	13.5	135.0	182.0	148.8	168.8	21	0.788	
Q1	1	141.8	140.2	14.8	113.0	174.9	132.0	148.0	21	0.969	0.012*
	2	138.3	137.7	10.6	116.8	161.3	129.5	143.8	22	0.998	
	3	136.1	136.5	14.3	99.8	167.5	127.5	148.5	22	0.697	
	4	125.8	127.5	10.4	111.1	141.8	119.0	137.3	21	0.089	
Q3	1	158.6	158.6	15.3	125.6	185.0	146.8	164.3	21	0.812	0.030*
	2	155.7	155.3	11.3	129.4	178.1	148.1	160.9	22	0.907	
	3	156.0	154.0	15.5	114.0	183.6	147.5	162.5	22	0.458	
	4	146.0	145.9	11.1	124.9	166.0	143.2	151.9	21	0.369	

Table 5c
Summary Statistics and Tests for Summary Measures and Drug
Original Data Set: Diastolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-3.3	-3.4	4.7	-11.3	5.1	-7.1	0.5	20	0.801	<0.001*
	2	-2.0	-1.5	4.7	-7.2	14.7	-4.4	-0.2	21	0.001*	
	3	-7.4	-6.1	5.3	-13.0	9.8	-10.1	-2.7	22	0.036*	
	4	-6.9	-7.6	5.0	-21.0	1.4	-9.6	-5.1	21	0.196	
MEAN	1	94.6	94.1	8.1	77.7	109.8	92.6	97.4	21	0.102	0.015*
	2	93.8	94.0	6.3	83.2	105.4	89.8	98.1	22	0.608	
	3	90.7	90.2	7.9	70.8	102.5	84.5	97.0	22	0.552	
	4	89.2	88.0	7.4	77.4	102.7	81.2	91.9	21	0.293	
MEDIAN	1	96.1	96.1	8.2	78.8	113.3	92.6	99.3	21	0.509	0.029*
	2	95.8	94.9	7.2	79.2	107.8	88.6	99.1	22	0.802	
	3	90.6	91.6	8.2	69.5	104.8	86.7	96.8	22	0.491	
	4	91.4	89.7	6.8	77.9	102.0	84.1	94.3	21	0.755	
MIN	1	73.0	72.2	10.3	49.0	98.0	66.0	79.5	21	0.626	0.006*
	2	73.0	73.8	7.2	62.5	89.0	68.0	78.5	22	0.701	
	3	70.0	69.7	9.1	51.0	87.0	63.5	75.0	22	0.969	
	4	65.0	64.0	11.1	42.0	90.5	57.0	69.0	21	0.516	
MAX	1	113.7	112.0	10.2	86.5	124.5	108.8	120.5	21	0.019*	0.002*
	2	115.1	115.6	11.0	99.7	140.0	107.8	121.5	22	0.462	
	3	106.6	106.4	8.2	93.8	119.0	98.0	113.5	22	0.077	
	4	105.3	105.6	8.5	93.0	125.5	98.7	110.7	21	0.608	
Q1	1	84.3	85.6	8.6	70.3	106.6	81.0	88.8	21	0.412	0.086
	2	86.5	86.4	7.3	69.8	98.3	81.3	90.6	22	0.806	
	3	84.5	83.9	9.0	62.8	97.5	79.3	90.8	22	0.411	
	4	77.4	80.4	8.0	67.3	95.5	75.1	84.9	21	0.233	
Q3	1	104.3	102.0	8.9	82.0	115.7	98.5	108.3	21	0.050	0.026*
	2	101.7	101.1	7.1	88.4	113.8	94.6	105.5	22	0.699	
	3	97.3	97.5	8.5	77.9	112.6	92.3	103.0	22	0.959	
	4	95.8	95.6	7.5	82.8	109.0	90.8	100.3	21	0.856	

Table 5d
Summary Statistics and Tests for Summary Measures and Therapy
Original Data Set: Dietary Response

SM	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	group1	-0.1	-0.1	0.1	-0.2	0.1	-0.1	0.0	8	0.527	<0.001*
	group2	-0.3	-0.2	0.1	-0.5	-0.1	-0.3	-0.1	8	0.589	
	group3	-0.4	-0.4	0.1	-0.5	-0.3	-0.5	-0.4	8	0.679	
MEAN	group1	0.9	0.9	0.1	0.8	1.0	0.8	1.0	8	0.386	<0.001*
	group2	0.8	0.8	0.1	0.7	0.8	0.7	0.8	8	0.250	
	group3	0.6	0.6	0.0	0.5	0.6	0.6	0.6	8	0.498	
MEDIAN	group1	0.9	0.9	0.1	0.8	1.0	0.8	1.0	8	0.235	<0.001*
	group2	0.7	0.8	0.1	0.7	0.9	0.7	0.8	8	0.241	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.6	8	0.934	
MIN	group1	0.7	0.8	0.1	0.6	0.9	0.7	0.8	8	0.638	<0.001*
	group2	0.6	0.6	0.1	0.5	0.7	0.5	0.7	8	0.217	
	group3	0.4	0.4	0.0	0.4	0.5	0.4	0.5	8	0.574	
MAX	group1	1.1	1.1	0.1	0.9	1.2	1.0	1.1	8	0.060	<0.001*
	group2	0.9	0.9	0.1	0.8	1.0	0.9	1.0	8	0.402	
	group3	0.8	0.8	0.1	0.6	0.9	0.8	0.8	8	0.335	
Q1	group1	0.8	0.8	0.1	0.7	1.0	0.8	0.9	8	0.937	<0.001*
	group2	0.7	0.7	0.1	0.6	0.7	0.6	0.7	8	0.665	
	group3	0.5	0.5	0.0	0.4	0.5	0.5	0.5	8	0.676	
Q3	group1	1.0	1.0	0.1	0.9	1.0	0.9	1.0	8	0.526	<0.001*
	group2	0.8	0.8	0.1	0.8	1.0	0.8	0.9	8	0.307	
	group3	0.6	0.7	0.1	0.5	0.8	0.6	0.7	8	0.726	

Table 6a
Summary Statistics and Tests for Summary Measures and Drug
Original Data Set: Heart Rate: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.5	2.0	4.8	-2.9	12.1	-1.0	3.4	12	0.025*	0.467
	2	2.3	2.5	3.3	-3.1	9.5	0.3	4.6	12	0.906	
	3	1.1	0.5	3.6	-5.8	6.6	-2.3	2.5	12	0.867	
	4	2.8	2.2	3.3	-2.9	7.4	-0.3	3.9	12	0.453	
MEAN	1	79.5	78.1	7.9	66.0	90.2	70.6	83.9	12	0.395	0.883
	2	78.6	76.7	8.7	64.4	91.4	70.2	83.2	13	0.616	
	3	78.0	78.2	9.1	65.8	91.9	69.1	85.4	12	0.327	
	4	76.4	75.9	6.3	64.8	88.1	71.9	80.0	12	0.998	
MEDIAN	1	78.1	76.7	8.6	64.5	90.0	69.0	83.5	12	0.448	0.832
	2	75.8	74.3	8.1	60.3	88.0	68.6	78.3	13	0.819	
	3	77.6	77.0	9.6	62.8	90.1	67.2	85.3	12	0.377	
	4	74.1	74.6	6.9	64.4	89.0	69.8	78.3	12	0.783	
MIN	1	64.0	62.7	8.4	49.5	76.0	56.8	68.3	12	0.538	0.767
	2	60.8	60.3	9.0	50.0	79.0	52.0	64.5	13	0.297	
	3	63.3	63.5	8.6	51.5	77.3	56.0	70.1	12	0.689	
	4	61.0	61.3	6.0	50.0	70.0	57.9	65.8	12	0.887	
MAX	1	105.0	103.2	13.3	81.0	123.0	94.1	114.0	12	0.297	0.884
	2	107.5	107.7	22.6	83.3	173.0	93.5	110.7	13	0.004*	
	3	102.8	101.1	11.3	85.5	118.5	89.5	110.0	12	0.351	
	4	99.1	101.4	11.4	89.0	122.7	92.6	107.6	12	0.090	
Q1	1	70.0	70.0	7.4	61.0	82.6	63.0	76.1	12	0.208	0.706
	2	68.0	67.7	8.9	56.3	84.4	59.8	72.6	13	0.295	
	3	72.5	71.2	8.8	58.3	84.5	64.3	76.8	12	0.652	
	4	67.8	68.6	7.6	55.5	80.1	64.0	74.4	12	0.888	
Q3	1	85.4	84.8	9.8	69.0	101.7	76.8	91.9	12	0.930	0.759
	2	83.8	84.6	11.1	66.3	99.3	76.8	94.0	13	0.547	
	3	83.8	83.9	11.2	67.8	99.8	75.1	93.7	12	0.408	
	4	81.3	81.0	6.5	68.6	94.0	76.8	84.9	12	0.970	

Table 6a cont.
Original Data Set: Heart Rate: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	0.5	2.2	-2.7	4.4	-1.2	1.6	8	0.919	0.103
	2	2.3	-0.6	6.1	-12.0	4.8	-1.6	3.6	9	0.021*	
	3	2.4	2.0	5.5	-10.2	11.2	0.4	4.5	10	0.222	
	4	4.5	5.2	5.7	-2.9	17.8	3.7	6.9	9	0.183	
MEAN	1	72.0	70.8	6.4	59.2	81.8	66.9	72.7	9	0.919	0.630
	2	68.7	71.1	11.6	49.2	85.8	67.6	80.7	9	0.480	
	3	72.0	69.0	13.4	48.4	85.0	60.8	80.7	10	0.254	
	4	73.3	75.1	5.3	69.9	86.7	71.1	77.2	9	0.104	
MEDIAN	1	70.5	69.9	6.3	58.8	78.5	67.1	72.5	9	0.866	0.497
	2	68.0	70.9	11.9	48.1	88.4	66.4	78.5	9	0.565	
	3	71.5	68.6	13.9	48.3	85.8	56.5	81.0	10	0.350	
	4	75.3	75.5	5.2	68.5	86.4	71.4	77.4	9	0.436	
MIN	1	61.0	60.0	5.3	51.5	68.5	57.5	63.5	9	0.966	0.360
	2	56.5	57.7	8.6	43.5	69.0	52.0	66.0	9	0.798	
	3	57.8	55.6	8.6	40.0	64.5	52.3	62.5	10	0.134	
	4	62.0	62.3	4.3	57.0	71.5	61.0	62.0	9	0.137	
MAX	1	90.8	90.5	13.0	71.0	118.0	84.0	93.0	9	0.489	0.836
	2	89.5	93.5	17.1	65.3	118.5	86.0	108.0	9	0.898	
	3	87.6	86.4	17.5	54.5	104.7	76.0	104.0	10	0.264	
	4	89.8	92.3	11.5	78.5	113.0	82.8	95.5	9	0.495	
Q1	1	68.0	66.3	5.9	55.3	74.0	63.3	68.5	9	0.697	0.843
	2	65.4	65.4	10.9	45.4	79.8	60.9	75.5	9	0.822	
	3	67.2	62.3	10.8	44.4	73.5	54.8	71.0	10	0.079	
	4	65.8	68.1	4.1	64.5	76.5	65.5	69.0	9	0.025*	
Q3	1	75.1	74.2	6.7	61.9	86.0	70.8	76.6	9	0.925	0.481
	2	73.3	75.4	12.2	51.6	93.8	71.1	83.4	9	0.517	
	3	77.8	74.6	15.8	50.6	93.9	61.6	88.1	10	0.281	
	4	79.5	80.9	6.3	72.6	93.5	76.6	84.3	9	0.651	

Table 6b

Summary Statistics and Tests for Summary Measures and Drug

Original Data Set: Systolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.2	-0.8	3.9	-10.9	2.9	-1.5	2.3	12	0.015*	0.002*
	2	-3.8	-2.1	7.8	-11.4	19.9	-6.8	-0.2	12	0.003*	
	3	-5.6	-8.3	6.8	-21.8	-0.5	-14.4	-3.6	12	0.157	
	4	-13.3	-13.3	11.2	-32.2	2.7	-19.9	-5.5	12	0.717	
MEAN	1	148.3	151.0	12.2	137.6	173.1	140.7	158.7	12	0.209	0.025*
	2	146.9	146.8	10.3	132.9	170.8	139.7	151.7	13	0.428	
	3	141.5	144.1	16.7	108.2	175.9	136.3	154.1	12	0.612	
	4	137.9	135.4	9.7	119.8	150.1	128.4	141.9	12	0.471	
MEDIAN	1	151.9	153.4	12.8	137.6	177.0	143.6	159.9	12	0.396	0.016*
	2	148.5	148.1	11.3	130.5	173.9	140.9	152.2	13	0.690	
	3	143.5	144.7	16.2	108.6	175.3	139.1	155.0	12	0.458	
	4	138.4	136.5	9.3	119.5	148.5	129.4	142.9	12	0.336	
MIN	1	121.3	123.5	8.5	112.5	139.0	116.8	130.0	12	0.537	0.188
	2	120.5	120.7	12.7	99.0	148.0	114.0	128.0	13	0.775	
	3	123.3	123.6	19.3	90.5	162.0	115.0	129.8	12	0.692	
	4	108.0	111.1	14.2	83.0	132.0	103.3	121.8	12	0.656	
MAX	1	170.2	173.0	14.6	153.8	196.5	165.5	182.5	12	0.072	0.042*
	2	171.0	171.7	11.2	158.0	196.5	162.0	176.8	13	0.281	
	3	160.3	163.6	17.2	133.0	201.5	153.8	174.4	12	0.613	
	4	159.4	159.1	12.0	138.5	182.0	151.3	166.8	12	0.881	
Q1	1	142.2	142.4	11.2	127.5	163.0	133.1	150.3	12	0.763	0.029*
	2	137.8	137.8	10.9	121.5	161.3	129.5	142.4	13	0.797	
	3	136.1	137.2	17.4	99.8	167.5	125.8	148.9	12	0.771	
	4	125.6	126.9	10.3	112.1	141.8	118.5	136.1	12	0.402	
Q3	1	158.9	160.0	13.5	143.1	185.0	149.3	168.2	12	0.573	0.017*
	2	157.5	156.3	9.7	142.0	178.1	149.3	160.4	13	0.645	
	3	148.2	151.4	16.8	114.0	183.5	145.9	160.8	12	0.394	
	4	145.9	143.7	9.3	124.9	156.0	137.8	150.1	12	0.117	

Table 6b cont.

Original Data Set: Systolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-6.8	-7.2	4.2	-14.8	-2.1	-9.6	-3.9	8	0.660	0.061
	2	-3.6	-3.4	5.4	-11.2	4.5	-7.4	-0.7	9	0.629	
	3	-6.5	-5.2	6.9	-15.7	10.0	-7.9	-1.5	10	0.358	
	4	-8.5	-11.2	5.7	-21.4	-6.5	-15.4	-7.0	9	0.024*	
MEAN	1	151.4	147.4	17.7	121.7	179.8	134.7	156.2	9	0.891	0.576
	2	143.2	145.6	12.1	122.3	162.6	140.9	154.0	9	0.792	
	3	146.3	147.0	11.4	131.0	168.7	140.0	151.0	10	0.852	
	4	143.6	138.5	11.8	119.5	151.4	131.3	148.0	9	0.327	
MEDIAN	1	150.5	149.7	16.8	121.6	177.9	138.6	159.4	9	0.998	0.455
	2	143.5	145.8	12.7	121.5	165.5	142.0	152.5	9	0.536	
	3	149.3	151.0	12.2	133.3	174.8	147.5	154.5	10	0.473	
	4	146.4	140.8	12.4	121.4	157.1	131.3	149.4	9	0.367	
MIN	1	116.0	120.6	21.2	91.5	166.5	108.5	124.0	9	0.290	0.135
	2	122.5	123.6	8.6	107.0	134.0	119.5	130.5	9	0.491	
	3	121.0	118.1	8.5	103.0	129.5	109.0	124.0	10	0.422	
	4	111.5	111.1	9.6	94.0	127.0	106.5	118.0	9	0.978	
MAX	1	174.3	170.7	23.4	130.0	203.0	157.5	183.0	9	0.906	0.621
	2	172.7	167.5	17.3	139.0	187.5	156.5	184.0	9	0.483	
	3	171.8	170.0	18.0	143.0	201.0	160.5	176.3	10	0.723	
	4	165.0	159.3	16.0	135.0	178.0	148.8	173.5	9	0.359	
Q1	1	135.0	137.3	19.0	113.0	174.9	122.5	146.5	9	0.591	0.380
	2	138.8	137.5	10.7	116.8	152.0	132.5	144.3	9	0.903	
	3	134.8	135.8	10.1	118.3	151.3	130.5	142.3	10	0.828	
	4	125.8	128.2	11.1	111.1	141.3	121.8	138.0	9	0.439	
Q3	1	158.6	156.7	18.2	125.6	185.0	144.3	164.3	9	0.992	0.691
	2	152.5	153.8	13.9	129.4	175.6	147.0	162.8	9	0.993	
	3	156.8	157.2	14.0	136.0	183.6	151.0	162.5	10	0.624	
	4	151.9	148.9	13.2	127.9	166.0	143.2	155.1	9	0.658	

Table 6c

Summary Statistics and Tests for Summary Measures and Drug

Original Data Set: Diastolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.5	-1.3	4.5	-9.0	5.1	-4.7	2.4	12	0.521	<0.001*
	2	-2.4	-0.9	5.8	-6.4	14.7	-4.5	0.4	12	0.005*	
	3	-9.1	-8.0	4.2	-13.0	0.4	-11.5	-5.4	12	0.341	
	4	-6.3	-7.8	6.2	-21.0	1.4	-11.8	-4.8	12	0.678	
MEAN	1	96.4	95.4	7.5	77.7	109.8	93.4	97.5	12	0.104	0.044*
	2	93.9	95.2	6.1	83.2	105.4	92.3	97.2	13	0.338	
	3	91.6	90.4	8.4	70.8	100.6	86.6	97.2	12	0.231	
	4	87.3	88.0	8.4	77.4	102.7	80.4	93.0	12	0.403	
MEDIAN	1	97.6	97.2	8.5	78.8	113.3	92.6	100.0	12	0.377	0.041*
	2	96.0	96.0	7.1	79.2	107.8	93.5	99.1	13	0.460	
	3	92.3	91.2	9.2	69.5	104.0	87.4	97.3	12	0.370	
	4	89.0	89.1	7.2	77.9	102.0	83.9	93.5	12	0.903	
MIN	1	74.5	72.7	7.6	60.3	84.0	66.8	79.5	12	0.632	0.189
	2	72.0	74.1	7.3	63.0	86.5	69.0	79.0	13	0.773	
	3	73.5	71.0	10.6	51.0	87.0	64.3	76.0	12	0.428	
	4	65.0	64.4	14.4	42.0	90.5	52.0	71.8	12	0.863	
MAX	1	114.5	114.3	8.7	91.0	124.5	112.8	120.8	12	0.017*	0.008*
	2	119.5	120.1	10.8	106.5	140.0	109.8	126.5	13	0.435	
	3	112.6	108.4	8.1	96.0	119.0	99.8	113.9	12	0.093	
	4	105.8	106.7	9.3	94.5	125.5	99.3	112.8	12	0.581	
Q1	1	85.8	86.2	8.4	73.8	106.6	81.0	89.6	12	0.250	0.427
	2	86.7	86.4	7.0	69.8	97.6	83.0	89.5	13	0.420	
	3	84.6	84.2	9.0	62.8	94.5	80.3	91.3	12	0.141	
	4	79.6	80.8	9.1	67.3	95.5	74.2	87.8	12	0.644	
Q3	1	105.3	103.9	8.3	83.3	115.7	101.8	108.8	12	0.103	0.017*
	2	103.0	103.1	6.4	94.1	113.8	98.0	105.5	13	0.474	
	3	97.5	97.3	8.4	77.9	109.3	93.6	102.6	12	0.524	
	4	94.5	95.2	7.6	82.8	109.0	90.3	98.9	12	0.900	

Table 6c cont.

Original Data Set: Diastolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-5.4	-6.5	3.3	-11.3	-3.0	-9.6	-3.8	8	0.216	0.034*
	2	-2.0	-2.2	3.1	-7.2	1.8	-3.4	-0.2	9	0.709	
	3	-6.2	-3.9	5.9	-9.4	9.8	-7.7	-1.3	10	0.039*	
	4	-6.9	-7.3	3.1	-13.6	-3.8	-9.2	-5.4	9	0.370	
MEAN	1	93.6	92.3	9.1	79.1	106.6	88.5	94.8	9	0.469	0.589
	2	93.4	92.3	6.6	84.0	100.8	87.4	98.1	9	0.285	
	3	86.9	89.9	7.8	81.9	102.5	83.7	94.5	10	0.085	
	4	89.2	88.1	6.4	78.4	99.1	84.9	91.7	9	0.660	
MEDIAN	1	94.8	94.5	8.2	80.8	106.5	93.0	97.3	9	0.634	0.735
	2	93.8	93.3	7.5	84.4	103.5	86.4	99.0	9	0.264	
	3	89.1	92.0	7.4	82.8	104.8	86.7	96.8	10	0.236	
	4	92.3	90.6	6.6	79.7	100.0	87.0	94.6	9	0.786	
MIN	1	68.0	71.4	13.6	49.0	98.0	65.5	78.0	9	0.672	0.059
	2	74.0	73.3	7.6	62.5	89.0	68.0	76.0	9	0.550	
	3	67.3	68.2	7.1	58.5	81.0	63.5	71.5	10	0.776	
	4	63.5	63.4	4.9	56.5	70.0	60.5	66.5	9	0.649	
MAX	1	112.0	108.8	11.8	86.5	123.0	100.8	116.5	9	0.543	0.341
	2	109.5	109.3	8.0	99.7	122.5	100.7	115.0	9	0.441	
	3	103.3	104.0	8.1	93.8	117.5	98.0	109.5	10	0.688	
	4	104.0	104.1	7.5	93.0	113.3	97.3	110.7	9	0.547	
Q1	1	84.0	84.7	9.4	70.3	102.5	81.0	88.8	9	0.953	0.357
	2	84.8	86.3	8.3	75.3	98.3	80.9	93.5	9	0.545	
	3	83.4	83.6	9.4	66.8	97.5	79.3	90.3	10	0.886	
	4	77.4	79.8	6.7	71.8	93.5	76.5	83.3	9	0.233	
Q3	1	101.5	99.4	9.6	82.0	110.8	95.8	107.0	9	0.553	0.805
	2	101.3	98.1	7.5	88.4	108.1	91.1	101.5	9	0.206	
	3	95.8	97.7	9.0	85.7	112.6	90.0	104.2	10	0.641	
	4	96.4	96.2	7.8	84.9	108.0	91.7	100.8	9	0.882	

Table 7a
Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Heart Rate

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	1.4	4.0	-3.5	12.1	-0.9	2.8	20	0.006*	0.173
	2	2.3	1.2	4.8	-12.0	9.5	-0.6	3.7	21	0.011*	
	3	1.3	1.3	4.7	-10.2	11.2	0.1	3.7	20	0.506	
	4	3.7	3.5	4.6	-2.9	18.1	1.3	5.8	21	0.010*	
MEAN	1	72.7	75.0	8.0	59.2	90.2	70.3	81.8	21	0.583	0.978
	2	74.1	74.4	10.1	49.2	91.4	67.6	83.2	22	0.488	
	3	77.8	73.5	11.8	48.4	91.9	66.6	81.1	20	0.142	
	4	75.4	75.6	5.8	64.8	88.1	71.8	78.9	21	0.639	
MEDIAN	1	72.5	73.8	8.3	58.8	90.0	67.3	81.1	21	0.766	0.931
	2	72.3	72.9	9.8	48.1	88.4	66.4	78.3	22	0.390	
	3	75.8	72.6	12.2	48.3	90.1	64.7	82.0	20	0.178	
	4	75.3	75.0	6.1	64.4	89.0	70.8	77.4	21	0.504	
MIN	1	61.0	61.6	7.2	49.5	76.0	57.0	67.5	21	0.799	0.586
	2	58.3	59.2	8.7	43.5	79.0	52.0	66.0	22	0.789	
	3	61.0	59.4	9.1	40.0	77.3	53.3	65.0	20	0.797	
	4	62.0	61.7	5.2	50.0	71.5	58.0	64.0	21	0.801	
MAX	1	98.3	97.8	14.3	71.0	123.0	86.0	106.7	21	0.656	0.743
	2	100.6	101.9	21.3	65.3	173.0	88.3	109.3	22	0.006*	
	3	100.4	94.3	15.8	54.5	118.5	85.9	104.8	20	0.131	
	4	94.8	97.5	12.1	78.5	122.7	89.8	105.7	21	0.400	
Q1	1	68.0	68.5	6.9	55.3	82.6	63.3	74.8	21	0.573	0.886
	2	66.7	66.8	9.8	45.4	84.4	59.8	74.6	22	0.861	
	3	69.4	66.4	10.3	44.4	83.7	58.4	73.4	20	0.199	
	4	66.8	68.4	6.1	55.5	80.1	65.3	72.8	21	0.429	
Q3	1	78.3	80.1	9.7	61.9	99.8	74.7	87.5	21	0.736	0.984
	2	80.9	80.8	12.1	51.6	99.3	72.2	91.5	22	0.469	
	3	82.2	79.0	14.0	50.6	99.8	68.9	88.5	20	0.235	
	4	80.9	81.0	6.3	68.6	94.0	76.6	84.5	21	0.729	

Table 7b
Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Systolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-2.5	-3.3	5.0	-14.8	2.9	-6.8	0.7	20	0.253	<0.001*
	2	-3.6	-2.6	6.8	-11.4	19.9	-6.9	-0.4	21	0.003*	
	3	-6.0	-6.8	6.8	-21.8	10.0	-10.2	-3.5	20	0.534	
	4	-9.1	-12.4	9.1	-32.2	2.7	-17.4	-6.5	21	0.273	
MEAN	1	150.9	149.5	14.4	121.7	179.8	138.4	156.2	21	0.983	0.016*
	2	146.8	146.3	10.8	122.3	170.8	139.7	154.0	22	0.996	
	3	143.6	145.4	14.8	108.2	176.2	138.5	152.3	20	0.633	
	4	138.0	136.7	10.5	119.5	151.1	131.3	143.8	21	0.146	
MEDIAN	1	150.5	151.8	14.3	121.6	177.9	141.1	159.4	21	0.824	0.012*
	2	146.4	147.3	11.7	121.5	173.9	140.9	152.5	22	0.976	
	3	147.6	147.6	15.0	108.6	175.6	139.9	153.7	20	0.324	
	4	139.6	138.3	10.7	119.5	157.1	131.3	146.8	21	0.349	
MIN	1	120.5	122.3	14.9	91.5	166.5	115.0	129.0	21	0.094	0.023*
	2	121.8	121.8	11.1	99.0	148.0	114.0	129.5	22	0.766	
	3	122.0	120.9	15.9	90.5	162.0	110.8	126.8	20	0.229	
	4	110.5	111.1	12.2	83.0	132.0	105.0	120.5	21	0.900	
MAX	1	170.8	172.0	18.4	130.0	203.0	165.5	183.0	21	0.473	0.063
	2	171.5	170.0	13.8	139.0	196.5	160.3	178.5	22	0.936	
	3	166.7	167.2	17.4	133.0	201.5	155.6	175.6	20	0.703	
	4	161.5	159.2	13.5	135.0	182.0	148.8	168.8	21	0.788	
Q1	1	141.8	140.6	14.7	113.0	174.9	132.3	148.0	21	0.981	0.013*
	2	138.3	137.7	10.6	116.8	161.3	129.5	143.8	22	0.997	
	3	136.1	136.1	14.9	99.8	168.1	125.8	146.0	20	0.889	
	4	125.8	127.5	10.5	111.1	142.0	119.0	137.3	21	0.099	
Q3	1	158.6	158.5	15.2	125.6	185.0	146.8	165.3	21	0.870	0.030*
	2	155.7	155.3	11.3	129.4	178.1	148.1	160.9	22	0.913	
	3	156.0	154.3	15.7	114.0	183.6	147.5	161.0	20	0.394	
	4	146.0	145.9	11.1	124.9	164.5	143.2	151.9	21	0.347	

Table 7c
Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Diastolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-3.1	-3.4	4.8	-11.3	5.3	-7.7	0.5	20	0.739	<0.001*
	2	-2.0	-1.4	4.8	-7.2	14.7	-4.4	-0.2	21	0.002*	
	3	-7.4	-6.2	5.2	-13.0	9.8	-9.8	-4.1	20	0.026*	
	4	-6.9	-7.6	5.0	-21.0	1.4	-9.6	-5.1	21	0.174	
MEAN	1	94.7	94.1	8.2	77.7	109.8	91.2	97.5	21	0.135	0.015*
	2	93.8	94.1	6.3	83.2	105.4	89.8	98.1	22	0.645	
	3	90.6	89.9	7.9	70.8	102.5	84.1	95.8	20	0.722	
	4	89.2	88.0	7.5	77.4	103.1	81.2	91.9	21	0.299	
MEDIAN	1	96.1	96.2	8.3	78.8	113.3	92.6	99.4	21	0.545	0.022*
	2	95.8	94.9	7.2	79.2	107.8	88.6	99.1	22	0.790	
	3	90.6	91.2	8.1	69.5	104.8	86.9	96.7	20	0.591	
	4	91.4	89.7	6.8	77.9	102.1	84.1	94.3	21	0.767	
MIN	1	73.0	72.2	10.3	49.0	98.0	66.0	79.5	21	0.626	0.008*
	2	73.0	73.8	7.2	62.5	89.0	68.0	78.5	22	0.701	
	3	70.8	69.7	9.5	51.0	87.0	62.3	76.0	20	0.934	
	4	65.0	64.0	11.1	42.0	90.5	57.0	69.0	21	0.516	
MAX	1	113.7	112.0	10.2	86.5	124.5	108.8	120.5	21	0.019*	0.002*
	2	115.1	115.6	11.0	99.7	140.0	107.8	121.5	22	0.462	
	3	106.6	106.4	7.6	95.0	117.5	98.0	113.1	20	0.055	
	4	105.3	105.6	8.5	93.0	125.5	98.7	110.7	21	0.608	
Q1	1	85.3	86.0	8.5	70.3	106.6	81.3	88.8	21	0.402	0.071
	2	86.9	86.5	7.3	69.8	98.3	81.3	90.6	22	0.794	
	3	84.6	83.4	9.2	62.8	97.5	77.6	90.5	20	0.560	
	4	77.4	80.4	8.1	67.3	96.6	75.1	84.9	21	0.270	
Q3	1	104.3	101.9	8.9	82.0	115.7	98.5	108.3	21	0.054	0.022*
	2	101.6	101.1	7.1	88.4	113.8	94.6	105.5	22	0.715	
	3	97.3	97.2	8.3	77.9	112.6	92.6	102.6	20	0.976	
	4	95.8	95.7	7.5	82.8	109.5	90.8	100.3	21	0.889	

Table 7d
Summary Statistics and Tests for Summary Measures and Therapy After Data Replaced: Dietary Response

SM	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	group1	-0.1	0.0	0.1	-0.2	0.1	-0.1	0.0	8	0.491	<0.001*
	group2	-0.3	-0.3	0.1	-0.5	-0.1	-0.3	-0.2	7	0.775	
	group3	-0.4	-0.4	0.1	-0.5	-0.3	-0.5	-0.4	7	0.855	
MEAN	group1	0.9	0.9	0.1	0.8	1.0	0.9	1.0	8	0.444	<0.001*
	group2	0.7	0.7	0.1	0.7	0.8	0.7	0.8	7	0.252	
	group3	0.6	0.6	0.0	0.5	0.6	0.6	0.6	7	0.795	
MEDIAN	group1	0.9	0.9	0.1	0.8	1.0	0.8	1.0	8	0.474	<0.001*
	group2	0.7	0.8	0.1	0.7	0.9	0.7	0.8	7	0.116	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.6	7	0.996	
MIN	group1	0.7	0.8	0.1	0.6	0.9	0.7	0.8	8	0.638	<0.001*
	group2	0.6	0.6	0.1	0.5	0.7	0.5	0.7	7	0.358	
	group3	0.4	0.4	0.1	0.4	0.5	0.4	0.5	7	0.546	
MAX	group1	1.1	1.1	0.1	0.9	1.2	1.0	1.1	8	0.060	<0.001*
	group2	0.9	0.9	0.1	0.8	1.0	0.9	0.9	7	0.457	
	group3	0.8	0.8	0.1	0.6	0.9	0.7	0.8	7	0.562	
Q1	group1	0.8	0.8	0.1	0.7	1.0	0.8	0.9	8	0.932	<0.001*
	group2	0.7	0.7	0.1	0.6	0.7	0.6	0.7	7	0.506	
	group3	0.5	0.5	0.0	0.5	0.5	0.5	0.5	7	0.884	
Q3	group1	1.0	1.0	0.1	0.9	1.0	0.9	1.0	8	0.526	<0.001*
	group2	0.8	0.8	0.1	0.8	0.9	0.8	0.9	7	0.279	
	group3	0.6	0.6	0.1	0.5	0.8	0.6	0.7	7	0.717	

Table 8a
Summary Statistics and Tests for Summary Measures and Drug
After Data Replaced: Average 3 Hrs Heart Rate

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	1.4	4.0	-3.5	12.1	-0.9	2.8	20	0.006*	0.173
	2	2.3	1.2	4.8	-12.0	9.5	-0.6	3.7	21	0.011*	
	3	1.3	1.3	4.7	-10.2	11.2	0.1	3.7	20	0.506	
	4	3.7	3.5	4.6	-2.9	18.1	1.3	5.8	21	0.010*	
MEAN	1	72.7	75.0	8.0	59.2	90.2	70.3	81.8	21	0.583	0.978
	2	74.1	74.4	10.1	49.2	91.4	67.6	83.2	22	0.488	
	3	77.8	73.5	11.8	48.4	91.9	66.6	81.1	20	0.142	
	4	75.4	75.6	5.8	64.8	88.1	71.8	78.9	21	0.639	
MEDIAN	1	72.4	74.8	8.5	60.0	92.2	68.7	82.4	21	0.720	0.917
	2	73.6	73.7	9.7	48.5	89.4	67.3	79.9	22	0.567	
	3	77.2	73.9	12.3	47.8	92.8	65.1	84.1	20	0.313	
	4	75.7	76.0	6.7	63.1	91.5	71.5	79.0	21	0.420	
MIN	1	64.7	65.6	6.5	53.5	77.0	60.5	70.7	21	0.709	0.667
	2	62.1	62.7	9.1	44.7	80.8	56.5	70.2	22	0.927	
	3	65.3	63.2	9.7	42.3	81.0	56.0	69.3	20	0.768	
	4	64.3	64.8	5.7	53.2	76.0	61.3	67.7	21	0.703	
MAX	1	82.8	86.0	10.3	67.3	108.2	79.8	91.9	21	0.739	0.902
	2	86.3	88.6	14.6	57.4	124.0	79.1	97.7	22	0.899	
	3	87.6	84.4	13.8	53.1	105.8	76.1	93.5	20	0.324	
	4	85.8	86.1	7.2	76.7	102.6	80.6	89.1	21	0.226	
Q1	1	69.1	69.2	7.2	55.2	84.8	63.8	75.2	21	0.630	0.806
	2	66.3	67.6	9.8	46.8	85.3	61.5	74.4	22	0.840	
	3	70.5	67.4	10.5	44.1	84.0	60.8	74.4	20	0.194	
	4	69.0	70.1	6.4	56.7	81.9	65.4	74.7	21	0.524	
Q3	1	76.4	79.9	9.5	61.3	97.8	74.5	86.4	21	0.590	0.984
	2	80.5	80.8	12.0	50.5	101.6	72.2	90.7	22	0.435	
	3	82.4	78.8	13.7	48.9	99.5	70.0	87.5	20	0.274	
	4	79.7	80.7	6.2	71.8	94.6	75.7	83.5	21	0.175	

Table 8b
Summary Statistics and Tests for Summary Measures and Drug
After Data Replaced: Average 3 Hrs Systolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-2.5	-3.3	5.0	-14.8	2.9	-6.8	0.7	20	0.253	<0.001*
	2	-3.6	-2.6	6.8	-11.4	19.9	-6.9	-0.4	21	0.003*	
	3	-6.0	-6.8	6.8	-21.8	10.0	-10.2	-3.5	20	0.534	
	4	-9.1	-12.4	9.1	-32.2	2.7	-17.4	-6.5	21	0.273	
MEAN	1	150.9	149.5	14.4	121.7	179.8	138.4	156.2	21	0.983	0.016*
	2	146.8	146.3	10.8	122.3	170.8	139.7	154.0	22	0.996	
	3	143.6	145.4	14.8	108.2	176.2	138.5	152.3	20	0.633	
	4	138.0	136.7	10.5	119.5	151.1	131.3	143.8	21	0.146	
MEDIAN	1	154.7	152.7	14.5	122.8	178.8	141.6	159.8	21	0.470	0.008*
	2	147.1	147.9	11.0	123.4	174.6	142.5	153.6	22	0.809	
	3	147.0	148.1	15.2	107.4	176.3	140.3	156.5	20	0.392	
	4	140.3	138.9	10.3	119.5	157.6	132.7	147.4	21	0.600	
MIN	1	128.5	129.3	15.2	99.8	171.0	120.2	135.0	21	0.343	0.020*
	2	131.7	129.8	11.3	108.5	156.3	119.8	136.0	22	0.494	
	3	128.2	127.8	16.1	98.7	166.7	114.0	134.6	20	0.596	
	4	116.2	118.1	12.4	87.8	139.0	111.5	127.7	21	0.684	
MAX	1	161.8	162.3	16.0	126.2	191.9	150.7	172.6	21	0.954	0.079
	2	159.9	159.8	11.7	137.3	178.6	152.3	165.7	22	0.589	
	3	159.5	158.7	16.3	116.7	188.1	150.0	165.5	20	0.355	
	4	151.9	151.0	12.6	127.8	174.0	145.6	159.2	21	0.580	
Q1	1	142.3	141.5	14.1	115.1	173.5	135.2	150.4	21	0.950	0.018*
	2	138.1	138.5	11.9	116.5	166.5	131.7	146.2	22	0.819	
	3	137.2	137.3	15.1	105.0	172.3	126.4	146.2	20	0.941	
	4	129.5	128.8	10.2	112.0	142.6	122.6	138.9	21	0.116	
Q3	1	157.4	157.8	15.3	124.5	185.3	147.9	165.9	21	0.971	0.018*
	2	154.4	154.2	11.6	126.4	175.8	147.3	160.4	22	0.930	
	3	152.7	153.1	16.2	112.6	183.1	145.4	160.6	20	0.478	
	4	145.3	144.7	11.0	124.9	162.7	139.8	150.2	21	0.473	

Table 8c

Summary Statistics and Tests for Summary Measures and Drug
After Data Replaced: Average 3 Hrs Diastolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-3.1	-3.4	4.8	-11.3	5.3	-7.7	0.5	20	0.739	<0.001*
	2	-2.0	-1.4	4.8	-7.2	14.7	-4.4	-0.2	21	0.002*	
	3	-7.4	-6.2	5.2	-13.0	9.8	-9.8	-4.1	20	0.026*	
	4	-6.9	-7.6	5.0	-21.0	1.4	-9.6	-5.1	21	0.174	
MEAN	1	94.7	94.1	8.2	77.7	109.8	91.2	97.5	21	0.135	0.015*
	2	93.8	94.1	6.3	83.2	105.4	89.8	98.1	22	0.645	
	3	90.6	89.9	7.9	70.8	102.5	84.1	95.8	20	0.722	
	4	89.2	88.0	7.5	77.4	103.1	81.2	91.9	21	0.299	
MEDIAN	1	97.5	96.6	8.4	76.8	111.2	94.3	100.5	21	0.082	0.022*
	2	96.8	95.5	6.7	83.1	106.9	92.4	98.5	22	0.521	
	3	91.6	92.7	8.4	71.2	107.5	88.3	97.8	20	0.535	
	4	92.2	90.4	6.6	80.1	102.6	84.3	94.2	21	0.473	
MIN	1	78.7	79.1	8.6	58.7	101.2	74.0	82.7	21	0.156	0.014*
	2	79.5	80.0	7.4	68.5	95.2	76.3	82.5	22	0.401	
	3	76.8	75.8	9.3	59.2	93.5	68.1	81.7	20	0.878	
	4	70.8	71.3	10.6	48.8	94.8	64.5	77.3	21	0.997	
MAX	1	107.3	104.4	9.3	83.5	116.8	100.4	111.1	21	0.018*	0.008*
	2	105.7	106.5	8.1	93.2	124.8	100.8	111.8	22	0.487	
	3	100.8	98.9	8.6	79.5	111.8	92.8	105.0	20	0.627	
	4	98.7	98.8	8.2	86.3	112.0	92.0	106.3	21	0.318	
Q1	1	86.8	87.3	9.0	69.1	108.0	82.9	90.8	21	0.483	0.069
	2	86.4	87.1	7.3	70.5	98.3	82.8	93.0	22	0.747	
	3	83.3	83.7	8.2	67.7	97.0	78.9	89.3	20	0.690	
	4	81.3	81.5	7.8	68.9	97.0	75.5	85.8	21	0.534	
Q3	1	102.0	100.6	8.6	80.8	115.1	98.6	104.8	21	0.037*	0.019*
	2	101.2	100.4	6.6	90.6	112.1	95.5	104.7	22	0.350	
	3	96.4	95.6	8.4	75.1	110.0	90.7	101.5	20	0.896	
	4	94.6	95.1	7.6	83.3	109.5	89.2	99.8	21	0.471	

Table 8d

After Data Replaced: Average 3 Hrs Dietary Response

SM	GROUP	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
BASE	group1	0.9	1.0	0.1	0.8	1.1	0.9	1.0	8	0.835	<0.001*
	group2	1.0	1.0	0.1	0.8	1.1	1.0	1.1	7	0.359	
	group3	1.0	1.0	0.1	0.9	1.1	1.0	1.1	7	0.749	
CHANGE	group1	-0.1	0.0	0.1	-0.2	0.1	-0.1	0.0	8	0.491	<0.001*
	group2	-0.3	-0.3	0.1	-0.5	-0.1	-0.3	-0.2	7	0.775	
	group3	-0.4	-0.4	0.1	-0.5	-0.3	-0.5	-0.4	7	0.855	
MEAN	group1	0.9	0.9	0.1	0.8	1.0	0.9	1.0	8	0.444	<0.001*
	group2	0.7	0.7	0.1	0.7	0.8	0.7	0.8	7	0.252	
	group3	0.6	0.6	0.0	0.5	0.6	0.6	0.6	7	0.795	
MEDIAN	group1	0.9	0.9	0.1	0.7	1.0	0.9	1.0	8	0.167	<0.001*
	group2	0.7	0.7	0.1	0.7	0.9	0.7	0.8	7	0.527	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.6	7	0.720	
MIN	group1	0.8	0.8	0.1	0.7	0.9	0.8	0.9	8	0.211	<0.001*
	group2	0.7	0.7	0.1	0.6	0.8	0.6	0.8	7	0.886	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.5	7	0.615	
MAX	group1	1.0	1.0	0.1	0.9	1.1	0.9	1.0	8	0.464	<0.001*
	group2	0.8	0.8	0.1	0.7	0.9	0.8	0.9	7	0.463	
	group3	0.7	0.7	0.1	0.6	0.8	0.6	0.7	7	0.707	
Q1	group1	0.8	0.8	0.1	0.7	0.9	0.8	0.9	8	0.211	<0.001*
	group2	0.7	0.7	0.1	0.6	0.8	0.6	0.8	7	0.886	
	group3	0.5	0.5	0.0	0.5	0.6	0.5	0.5	7	0.615	
Q3	group1	1.0	1.0	0.1	0.9	1.1	0.9	1.0	8	0.464	<0.001*
	group2	0.8	0.8	0.1	0.7	0.9	0.8	0.9	7	0.463	
	group3	0.7	0.7	0.1	0.6	0.8	0.6	0.7	7	0.707	

Table 9a
Summary Statistics and Tests for Summary Measures and Drug
After Data Replaced: Average 3 Hrs Heart Rate: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.5	2.0	4.9	-3.5	12.1	-0.9	3.6	12	0.054	0.550
	2	2.3	2.5	3.3	-3.1	9.5	0.3	4.6	12	0.908	
	3	1.1	0.7	3.7	-5.8	6.6	-3.3	2.9	11	0.658	
	4	2.9	2.2	3.3	-2.9	7.4	-0.3	3.9	12	0.431	
MEAN	1	79.1	78.0	7.9	66.0	90.2	70.6	83.9	12	0.474	0.902
	2	78.6	76.7	8.7	64.4	91.4	70.2	83.2	13	0.614	
	3	77.8	77.0	8.4	65.8	91.9	68.4	84.9	11	0.451	
	4	76.4	75.9	6.3	64.8	88.1	72.0	80.0	12	0.998	
MEDIAN	1	81.3	78.0	9.1	63.5	92.2	69.6	84.1	12	0.454	0.893
	2	76.3	75.4	8.3	59.1	89.4	70.4	79.5	13	0.943	
	3	77.8	76.7	9.0	63.9	92.8	69.1	85.2	11	0.855	
	4	75.1	76.0	7.1	63.1	91.5	72.0	79.5	12	0.808	
MIN	1	66.8	67.1	6.8	58.0	77.0	60.9	73.3	12	0.262	0.594
	2	65.6	63.5	8.8	52.1	80.8	57.0	67.8	13	0.505	
	3	67.7	66.4	8.5	55.0	81.0	57.3	73.4	11	0.760	
	4	63.6	64.6	6.9	53.2	76.0	60.5	69.9	12	0.933	
MAX	1	91.2	90.0	9.1	74.0	108.2	83.2	95.2	12	0.911	0.732
	2	90.0	92.4	13.9	71.5	124.0	83.1	97.7	13	0.667	
	3	87.7	88.4	9.8	74.9	105.8	80.1	96.5	11	0.755	
	4	86.3	87.4	8.0	76.7	102.6	81.0	91.8	12	0.630	
Q1	1	73.2	71.1	7.5	61.7	84.8	64.2	76.2	12	0.199	0.732
	2	68.9	68.8	9.1	57.5	85.3	61.8	74.1	13	0.192	
	3	73.0	71.3	7.4	60.5	84.0	65.0	76.2	11	0.803	
	4	69.7	70.5	7.6	56.7	81.9	65.1	75.7	12	0.915	
Q3	1	84.2	84.5	8.9	71.8	97.8	75.8	91.5	12	0.498	0.833
	2	83.8	84.8	10.4	70.8	101.6	78.2	92.5	13	0.563	
	3	82.5	82.6	10.2	67.8	99.5	72.7	89.2	11	0.706	
	4	80.9	81.1	5.9	72.3	93.7	77.3	83.7	12	0.806	

Table 9a cont
After Data Replaced: Average 3 Hrs Heart Rate: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	0.5	2.2	-2.6	4.4	-1.2	1.6	8	0.906	0.109
	2	2.3	-0.6	6.1	-12.0	4.8	-1.6	3.6	9	0.021*	
	3	2.2	2.0	5.8	-10.2	11.2	0.4	4.5	9	0.391	
	4	4.5	5.3	5.8	-2.9	18.1	3.7	6.9	9	0.164	
MEAN	1	72.0	70.8	6.4	59.2	81.8	66.9	72.7	9	0.920	0.691
	2	68.7	71.1	11.6	49.2	85.8	67.6	80.7	9	0.479	
	3	75.8	69.1	14.2	48.4	85.0	60.8	80.7	9	0.140	
	4	73.3	75.1	5.4	69.9	86.9	71.1	77.2	9	0.094	
MEDIAN	1	71.5	70.6	5.8	60.0	79.3	67.3	73.9	9	0.980	0.557
	2	69.0	71.3	11.5	48.5	85.8	66.9	79.9	9	0.319	
	3	76.6	70.5	15.3	47.8	87.3	60.0	83.3	9	0.203	
	4	75.7	76.1	6.4	68.8	89.6	70.8	77.8	9	0.325	
MIN	1	64.2	63.7	5.8	53.5	71.8	60.5	66.2	9	0.918	0.763
	2	59.8	61.5	9.9	44.7	74.0	56.5	70.3	9	0.754	
	3	63.7	59.2	10.1	42.3	69.7	54.3	67.5	9	0.137	
	4	64.3	65.1	3.9	60.2	73.8	63.5	65.7	9	0.147	
MAX	1	80.8	80.7	9.8	67.3	103.3	77.3	81.1	9	0.038*	0.749
	2	81.2	83.0	14.4	57.4	102.3	76.7	93.8	9	0.584	
	3	82.2	79.4	16.7	53.1	100.4	73.3	93.3	9	0.423	
	4	84.3	84.3	5.8	77.3	95.2	79.6	87.3	9	0.622	
Q1	1	67.1	66.8	6.3	55.2	75.8	63.1	69.3	9	0.948	0.834
	2	65.3	66.0	11.0	46.8	80.7	61.5	76.9	9	0.755	
	3	69.2	62.6	12.1	44.1	76.3	55.1	70.7	9	0.204	
	4	68.7	69.6	4.7	64.7	79.0	66.9	69.5	9	0.109	
Q3	1	74.5	73.8	6.7	61.3	84.9	70.2	76.4	9	0.922	0.587
	2	73.8	75.1	12.4	50.5	92.8	71.0	83.7	9	0.540	
	3	80.0	74.1	16.6	48.9	92.5	64.3	87.3	9	0.157	
	4	79.3	80.1	6.8	71.8	94.6	74.8	83.5	9	0.387	

Table 9b

Summary Statistics and Tests for Summary Measures and Drug

After Data Replaced: Average 3 Hrs Systolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.2	-0.8	3.8	-10.3	2.9	-2.3	2.3	12	0.057	0.003*
	2	-3.8	-2.0	7.8	-11.4	19.9	-6.8	0.0	12	0.004*	
	3	-5.6	-7.6	6.7	-21.8	-0.5	-12.9	-3.4	11	0.100	
	4	-13.0	-13.3	11.1	-32.2	2.7	-19.9	-5.5	12	0.743	
MEAN	1	148.4	151.0	11.9	137.6	171.5	140.9	158.7	12	0.201	0.023*
	2	147.3	146.8	10.3	132.9	170.8	139.7	151.7	13	0.426	
	3	141.3	143.2	17.2	108.2	176.2	135.6	153.7	11	0.562	
	4	137.9	135.5	9.8	119.8	151.1	128.4	141.9	12	0.538	
MEDIAN	1	152.7	154.3	13.2	138.4	178.2	143.9	162.0	12	0.238	0.006*
	2	150.6	149.2	10.2	132.6	174.6	142.5	153.6	13	0.199	
	3	143.5	143.9	16.6	107.4	174.7	138.8	153.7	11	0.367	
	4	139.2	137.0	9.3	119.5	149.7	130.4	143.1	12	0.580	
MIN	1	129.3	131.4	10.4	117.5	152.0	123.8	137.6	12	0.367	0.073
	2	130.5	129.8	12.9	110.0	156.3	119.2	136.0	13	0.753	
	3	133.4	132.0	19.9	98.7	166.7	115.8	148.3	11	0.994	
	4	115.4	117.9	13.9	87.8	139.0	111.7	128.4	12	0.602	
MAX	1	161.5	163.2	13.3	144.3	186.8	152.4	171.8	12	0.389	0.101
	2	162.3	159.9	9.2	143.3	176.7	153.1	164.6	13	0.925	
	3	153.0	154.9	17.3	116.7	186.5	148.2	166.5	11	0.229	
	4	151.8	150.3	11.9	130.5	174.0	143.8	156.1	12	0.372	
Q1	1	141.7	143.1	10.8	127.2	162.8	136.1	151.1	12	0.945	0.047*
	2	136.9	138.4	12.8	120.4	166.5	131.7	144.1	13	0.554	
	3	134.9	136.9	18.4	105.0	172.3	125.9	149.1	11	0.991	
	4	129.6	128.3	10.0	112.0	142.6	120.1	137.2	12	0.674	
Q3	1	156.3	159.2	13.3	140.2	183.2	149.6	169.0	12	0.512	0.007*
	2	155.3	155.0	9.5	140.6	175.8	149.0	159.6	13	0.736	
	3	146.5	148.5	17.0	112.6	181.1	142.6	156.3	11	0.405	
	4	145.3	142.4	9.4	124.9	155.4	135.6	148.9	12	0.172	

Table 9b cont

After Data Replaced: Average 3 Hrs Systolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-6.8	-7.1	4.3	-14.8	-2.1	-9.6	-3.6	8	0.609	0.065
	2	-3.6	-3.4	5.4	-11.2	4.5	-7.4	-0.7	9	0.630	
	3	-6.6	-5.8	7.3	-15.7	10.0	-8.5	-5.2	9	0.252	
	4	-8.5	-11.2	5.6	-21.4	-6.5	-15.4	-7.0	9	0.026*	
MEAN	1	151.4	147.5	17.7	121.7	179.8	134.7	156.2	9	0.885	0.538
	2	143.2	145.6	12.1	122.3	162.6	140.9	154.0	9	0.793	
	3	147.2	148.2	11.6	129.2	168.7	140.9	151.0	9	0.935	
	4	143.6	138.4	11.8	119.5	151.1	131.3	148.0	9	0.298	
MEDIAN	1	156.0	150.7	16.6	122.8	178.8	140.0	159.8	9	0.798	0.293
	2	144.6	146.0	12.5	123.4	164.7	140.9	152.2	9	0.726	
	3	150.8	153.1	12.4	131.8	176.3	146.3	157.8	9	0.846	
	4	145.9	141.4	11.7	123.6	157.6	133.9	149.5	9	0.496	
MIN	1	120.2	126.5	20.3	99.8	171.0	115.2	134.3	9	0.282	0.114
	2	132.8	129.9	9.2	108.5	138.5	129.5	134.7	9	0.038*	
	3	127.0	122.7	8.4	111.4	131.3	112.2	129.2	9	0.018*	
	4	118.5	118.4	10.9	100.8	133.0	111.5	124.8	9	0.816	
MAX	1	161.8	161.2	19.9	126.2	191.9	149.6	172.6	9	0.996	0.504
	2	155.5	159.8	15.2	137.3	178.6	148.8	175.9	9	0.424	
	3	163.0	163.3	14.4	136.2	188.1	157.4	164.4	9	0.377	
	4	159.2	152.0	14.2	127.8	168.8	145.6	161.2	9	0.287	
Q1	1	142.3	139.4	18.1	115.1	173.5	125.4	147.9	9	0.740	0.428
	2	139.3	138.6	11.2	116.5	154.3	135.2	146.2	9	0.790	
	3	138.4	137.7	10.8	123.0	155.8	127.4	142.3	9	0.827	
	4	129.4	129.5	11.1	112.9	142.5	122.9	139.7	9	0.308	
Q3	1	159.3	156.0	18.3	124.5	185.3	142.7	165.9	9	0.964	0.520
	2	153.4	153.0	14.7	126.4	173.0	146.3	160.8	9	0.915	
	3	155.5	158.8	14.0	134.3	183.1	153.0	160.8	9	0.456	
	4	150.1	147.6	12.7	127.0	162.7	139.8	155.5	9	0.581	

Table 9c

Summary Statistics and Tests for Summary Measures and Drug
After Data Replaced: Average 3 Hrs Diastolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.5	-1.4	4.7	-9.0	5.3	-5.1	2.4	12	0.388	0.002*
	2	-2.4	-0.9	5.8	-6.4	14.7	-4.5	0.8	12	0.006*	
	3	-8.0	-7.7	4.3	-13.0	0.4	-11.5	-5.3	11	0.596	
	4	-6.3	-7.8	6.2	-21.0	1.4	-11.6	-4.8	12	0.651	
MEAN	1	96.4	95.3	7.5	77.7	109.8	92.8	97.6	12	0.145	0.038*
	2	93.9	95.3	6.1	83.2	105.4	92.3	97.2	13	0.393	
	3	91.4	89.4	8.1	70.8	98.9	84.7	97.0	11	0.185	
	4	87.3	88.0	8.5	77.4	103.1	80.4	93.0	12	0.411	
MEDIAN	1	98.3	98.2	8.3	76.8	111.2	96.9	101.4	12	0.033*	0.017*
	2	97.2	96.8	5.9	83.5	106.9	93.8	98.3	13	0.601	
	3	91.1	91.2	8.3	71.2	101.4	86.4	98.2	11	0.154	
	4	90.7	90.2	6.9	80.1	102.6	83.8	94.5	12	0.795	
MIN	1	79.2	79.8	5.5	72.2	93.0	76.6	82.6	12	0.191	0.230
	2	78.8	80.3	7.4	68.7	95.2	76.3	82.5	13	0.891	
	3	79.2	78.0	10.8	59.2	93.5	66.5	87.3	11	0.572	
	4	72.2	71.6	13.2	48.8	94.8	60.2	79.3	12	0.972	
MAX	1	107.6	106.1	8.3	84.1	116.8	104.1	110.5	12	0.034*	0.009*
	2	107.4	109.5	7.9	100.0	124.8	103.8	112.5	13	0.200	
	3	101.6	98.9	9.1	79.5	108.8	90.6	105.5	11	0.195	
	4	96.3	98.1	8.5	86.3	112.0	91.4	103.9	12	0.504	
Q1	1	87.2	87.8	8.7	74.1	108.0	82.8	92.1	12	0.366	0.233
	2	87.1	87.4	7.3	70.5	98.3	85.5	92.6	13	0.399	
	3	83.4	83.5	7.7	67.7	94.3	81.4	89.6	11	0.539	
	4	80.5	81.7	9.0	68.9	97.0	74.9	88.2	12	0.687	
Q3	1	103.3	102.4	7.8	82.0	115.1	100.7	105.0	12	0.020*	0.014*
	2	102.8	102.1	6.1	92.0	112.1	96.3	104.7	13	0.613	
	3	97.1	94.7	8.4	75.1	105.0	90.1	101.4	11	0.189	
	4	93.7	95.2	8.4	83.3	109.5	89.0	99.5	12	0.418	

Table 9c cont.

After Data Replaced: Average 3 Hrs Diastolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-5.4	-6.4	3.3	-11.3	-3.0	-9.6	-3.7	8	0.213	0.036*
	2	-2.0	-2.2	3.1	-7.2	1.8	-3.4	-0.2	9	0.707	
	3	-7.3	-4.5	6.0	-9.4	9.8	-7.7	-3.1	9	0.009*	
	4	-6.9	-7.3	3.1	-13.6	-3.8	-9.2	-5.4	9	0.365	
MEAN	1	93.6	92.3	9.1	79.1	106.6	88.5	94.7	9	0.467	0.595
	2	93.4	92.3	6.6	84.0	100.8	87.4	98.1	9	0.283	
	3	88.3	90.4	8.2	81.2	102.5	83.7	94.5	9	0.185	
	4	89.2	88.1	6.4	78.4	99.1	84.8	91.7	9	0.663	
MEDIAN	1	94.8	94.4	8.5	78.6	105.4	92.4	97.9	9	0.590	0.712
	2	93.8	93.6	7.6	83.1	103.7	87.9	98.5	9	0.572	
	3	92.0	94.5	8.5	82.7	107.5	88.9	97.3	9	0.405	
	4	92.2	90.7	6.4	81.5	99.8	86.0	94.2	9	0.530	
MIN	1	74.7	78.1	11.9	58.7	101.2	73.2	86.2	9	0.381	0.098
	2	80.0	79.7	7.9	68.5	94.7	77.5	81.7	9	0.534	
	3	72.2	73.1	6.7	64.3	83.8	69.7	76.2	9	0.746	
	4	69.8	70.8	6.4	61.2	82.5	68.0	75.0	9	0.972	
MAX	1	106.3	102.2	10.6	83.5	113.6	97.7	111.4	9	0.301	0.712
	2	100.8	102.3	6.7	93.2	111.8	97.9	107.4	9	0.599	
	3	97.4	99.0	8.4	86.0	111.8	95.7	102.8	9	0.874	
	4	100.2	99.6	8.2	87.0	111.0	95.5	107.0	9	0.699	
Q1	1	86.8	86.7	9.8	69.1	103.9	82.9	89.0	9	0.838	0.430
	2	85.3	86.6	7.6	76.4	96.7	81.2	94.5	9	0.435	
	3	81.6	84.1	9.4	68.8	97.0	78.8	89.0	9	0.584	
	4	81.3	81.3	6.5	72.4	94.3	78.7	82.9	9	0.691	
Q3	1	101.5	98.1	9.5	80.8	109.8	93.6	103.9	9	0.688	0.764
	2	99.1	97.9	6.8	90.6	108.5	91.5	101.5	9	0.202	
	3	95.5	96.8	8.8	84.2	110.0	91.3	102.3	9	0.804	
	4	95.3	95.0	7.0	84.0	105.4	91.0	99.8	9	0.908	

Table 10a
Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Average 2 Hrs Heart Rate

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	1.4	4.0	-3.5	12.1	-0.9	2.8	20	0.006*	0.173
	2	2.3	1.2	4.8	-12.0	9.5	-0.6	3.7	21	0.011*	
	3	1.3	1.3	4.7	-10.2	11.2	0.1	3.7	20	0.506	
	4	3.7	3.5	4.6	-2.9	18.1	1.3	5.8	21	0.010*	
MEAN	1	72.7	75.0	8.0	59.2	90.2	70.3	81.8	21	0.583	0.978
	2	74.1	74.4	10.1	49.2	91.4	67.6	83.2	22	0.488	
	3	77.8	73.5	11.8	48.4	91.9	66.6	81.1	20	0.142	
	4	75.4	75.6	5.8	64.8	88.1	71.8	78.9	21	0.639	
MEDIAN	1	73.2	74.5	8.9	59.1	91.8	67.1	83.0	21	0.573	0.989
	2	74.1	73.8	9.9	48.3	90.6	68.3	79.4	22	0.495	
	3	76.4	73.0	12.1	48.0	88.6	65.1	82.4	20	0.115	
	4	75.2	75.1	5.8	66.5	88.7	70.9	77.5	21	0.331	
MIN	1	63.8	63.7	6.6	52.3	77.0	58.8	68.0	21	0.967	0.664
	2	61.5	61.6	8.8	44.3	79.3	56.0	68.5	22	0.992	
	3	64.1	61.4	9.2	41.3	79.7	54.5	66.9	20	0.455	
	4	63.5	64.1	5.8	52.3	76.0	61.3	67.3	21	0.833	
MAX	1	90.0	90.8	12.0	70.5	110.0	81.9	100.0	21	0.357	0.848
	2	95.8	91.8	14.1	61.0	124.4	81.8	101.0	22	0.789	
	3	88.5	87.1	15.0	52.3	110.6	79.3	96.1	20	0.525	
	4	88.5	90.8	9.9	78.4	112.5	83.4	94.4	21	0.041*	
Q1	1	68.7	69.2	7.3	55.4	85.5	63.5	75.1	21	0.569	0.796
	2	65.9	67.3	10.1	46.6	84.3	60.2	74.2	22	0.488	
	3	70.4	67.1	10.3	45.8	83.0	60.0	73.8	20	0.143	
	4	67.6	69.0	5.9	55.9	79.9	65.5	73.7	21	0.134	
Q3	1	77.1	79.3	9.3	61.1	97.1	74.8	86.7	21	0.741	0.906
	2	80.3	80.5	12.6	50.9	109.8	72.4	88.6	22	0.809	
	3	82.0	79.5	13.9	49.2	100.6	70.4	88.3	20	0.234	
	4	81.0	80.9	6.2	71.6	95.4	77.3	83.9	21	0.103	

Table 10b
Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Average 2 Hrs Systolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-2.5	-3.3	5.0	-14.8	2.9	-6.8	0.7	20	0.253	<0.001*
	2	-3.6	-2.6	6.8	-11.4	19.9	-6.9	-0.4	21	0.003*	
	3	-6.0	-6.8	6.8	-21.8	10.0	-10.2	-3.5	20	0.534	
	4	-9.1	-12.4	9.1	-32.2	2.7	-17.4	-6.5	21	0.273	
MEAN	1	150.9	149.5	14.4	121.7	179.8	138.4	156.2	21	0.983	0.016*
	2	146.8	146.3	10.8	122.3	170.8	139.7	154.0	22	0.996	
	3	143.6	145.4	14.8	108.2	176.2	138.5	152.3	20	0.633	
	4	138.0	136.7	10.5	119.5	151.1	131.3	143.8	21	0.146	
MEDIAN	1	153.6	152.6	14.0	122.2	177.7	140.6	159.6	21	0.879	0.006*
	2	147.8	148.1	11.3	123.1	171.0	142.4	155.4	22	0.962	
	3	148.4	148.0	15.1	107.0	175.3	140.8	154.3	20	0.265	
	4	139.2	138.7	10.0	118.9	152.8	133.5	147.1	21	0.303	
MIN	1	125.0	127.0	16.4	94.3	172.0	117.0	133.0	21	0.180	0.052
	2	128.9	127.1	11.4	107.8	156.8	118.0	134.3	22	0.116	
	3	127.8	125.9	16.2	98.8	165.0	115.0	131.9	20	0.376	
	4	114.0	116.8	13.1	83.8	141.5	110.5	126.5	21	0.663	
MAX	1	162.9	165.1	16.6	127.1	191.3	155.1	179.9	21	0.474	0.096
	2	164.5	163.4	12.4	136.5	185.3	156.8	168.4	22	0.820	
	3	164.1	161.6	17.5	119.0	192.1	151.7	168.3	20	0.368	
	4	154.3	153.7	14.2	126.4	178.0	147.8	163.5	21	0.395	
Q1	1	138.4	141.7	14.1	119.1	173.3	134.5	147.3	21	0.711	0.013*
	2	139.8	138.3	11.2	116.1	165.4	131.0	143.1	22	0.718	
	3	136.2	136.5	14.8	105.3	171.6	126.9	145.6	20	0.983	
	4	127.8	128.4	10.8	112.8	144.3	119.2	137.8	21	0.116	
Q3	1	160.3	158.1	15.4	123.3	186.9	149.4	165.6	21	0.947	0.016*
	2	154.0	153.9	11.8	127.3	176.1	146.0	161.1	22	0.961	
	3	154.6	153.6	16.4	111.5	185.2	145.8	161.5	20	0.513	
	4	144.8	144.8	10.7	125.8	164.5	138.8	150.9	21	0.571	

Table 10c

Summary Statistics and Tests for Summary Measures and Drug After Data Replaced: Average 2 Hrs Diastolic Blood Pressure

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-3.1	-3.4	4.8	-11.3	5.3	-7.7	0.5	20	0.739	<0.001*
	2	-2.0	-1.4	4.8	-7.2	14.7	-4.4	-0.2	21	0.002*	
	3	-7.4	-6.2	5.2	-13.0	9.8	-9.8	-4.1	20	0.026*	
	4	-6.9	-7.6	5.0	-21.0	1.4	-9.6	-5.1	21	0.174	
MEAN	1	94.7	94.1	8.2	77.7	109.8	91.2	97.5	21	0.135	0.015*
	2	93.8	94.1	6.3	83.2	105.4	89.8	98.1	22	0.645	
	3	90.6	89.9	7.9	70.8	102.5	84.1	95.8	20	0.722	
	4	89.2	88.0	7.5	77.4	103.1	81.2	91.9	21	0.299	
MEDIAN	1	97.3	96.2	8.1	79.3	113.3	93.5	99.3	21	0.201	0.037*
	2	95.4	95.0	6.8	82.2	107.7	90.8	100.3	22	0.890	
	3	91.3	91.9	8.3	70.3	106.1	87.4	97.6	20	0.551	
	4	91.8	90.2	6.6	78.8	101.6	84.7	95.3	21	0.638	
MIN	1	77.3	76.8	10.2	53.0	100.3	70.3	81.3	21	0.616	0.118
	2	76.9	77.4	6.8	64.5	91.0	73.8	80.8	22	0.509	
	3	76.0	74.4	8.8	61.3	91.8	67.0	80.0	20	0.462	
	4	69.3	70.3	12.1	45.3	96.0	63.3	80.5	21	0.969	
MAX	1	109.6	106.9	10.1	83.8	120.1	102.3	112.6	21	0.052	0.006*
	2	109.8	109.4	8.8	94.3	128.5	104.0	114.5	22	0.744	
	3	104.9	101.8	8.6	80.3	115.5	95.8	107.1	20	0.410	
	4	99.4	100.8	7.9	86.5	116.1	95.7	104.6	21	0.736	
Q1	1	88.1	87.2	8.8	70.0	103.4	83.0	91.9	21	0.861	0.033*
	2	86.6	87.3	7.3	70.4	98.4	82.1	93.2	22	0.641	
	3	84.6	83.5	8.2	66.4	95.8	79.0	88.8	20	0.294	
	4	79.4	81.2	7.5	72.2	98.4	75.0	84.1	21	0.099	
Q3	1	102.1	101.0	8.4	81.9	115.3	99.8	106.2	21	0.094	0.021*
	2	100.7	100.5	7.2	89.9	114.9	94.7	105.8	22	0.332	
	3	96.7	96.2	8.5	74.2	112.1	90.6	102.6	20	0.768	
	4	94.0	94.6	7.8	81.4	107.6	87.4	100.0	21	0.619	

Table 11a

Summary Statistics and Tests for Summary Measures and Drug

After Data Replaced: Average 2 Hrs Heart Rate: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.5	2.0	4.9	-3.5	12.1	-0.9	3.6	12	0.054	0.550
	2	2.3	2.5	3.3	-3.1	9.5	0.3	4.6	12	0.908	
	3	1.1	0.7	3.7	-5.8	6.6	-3.3	2.9	11	0.658	
	4	2.9	2.2	3.3	-2.9	7.4	-0.3	3.9	12	0.431	
MEAN	1	79.1	78.0	7.9	66.0	90.2	70.6	83.9	12	0.474	0.902
	2	78.6	76.7	8.7	64.4	91.4	70.2	83.2	13	0.614	
	3	77.8	77.0	8.4	65.8	91.9	68.4	84.9	11	0.451	
	4	76.4	75.9	6.3	64.8	88.1	72.0	80.0	12	0.998	
MEDIAN	1	80.3	77.6	9.4	63.8	91.8	68.2	83.7	12	0.336	0.862
	2	77.0	75.4	8.7	59.9	90.6	70.7	78.3	13	0.626	
	3	77.5	75.7	8.7	63.4	88.6	65.9	82.5	11	0.584	
	4	74.1	74.9	6.6	66.5	88.7	70.5	78.4	12	0.623	
MIN	1	64.9	64.6	7.5	52.3	77.0	58.0	70.1	12	0.816	0.786
	2	61.8	62.3	8.6	51.5	79.3	56.7	66.0	13	0.413	
	3	65.5	64.0	8.1	52.7	79.7	55.5	70.1	11	0.778	
	4	62.9	63.6	6.8	52.3	76.0	59.8	67.9	12	0.968	
MAX	1	96.5	95.3	10.9	75.8	110.0	88.4	104.9	12	0.518	0.543
	2	97.3	96.6	12.6	75.0	124.4	87.1	104.4	13	0.699	
	3	89.3	91.2	10.8	77.4	110.6	81.6	94.0	11	0.117	
	4	89.8	92.3	9.9	79.5	112.5	87.0	95.7	12	0.197	
Q1	1	71.2	70.9	7.6	62.0	85.5	63.8	76.8	12	0.157	0.638
	2	68.0	68.0	9.1	57.0	84.3	60.2	72.9	13	0.129	
	3	72.9	70.5	7.7	59.8	83.0	63.9	74.4	11	0.563	
	4	67.8	69.6	7.2	55.9	79.9	65.5	75.1	12	0.593	
Q3	1	86.2	84.2	8.4	70.6	97.1	76.3	90.7	12	0.685	0.847
	2	82.0	84.8	11.8	67.8	109.8	76.1	92.2	13	0.831	
	3	82.5	83.6	10.2	69.6	100.6	73.9	90.5	11	0.807	
	4	81.1	81.2	5.7	71.6	94.7	77.4	84.1	12	0.365	

Table 11a cont.

After Data Replaced: Average 2 Hrs Heart Rate: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	0.6	0.5	2.2	-2.6	4.4	-1.2	1.6	8	0.906	0.109
	2	2.3	-0.6	6.1	-12.0	4.8	-1.6	3.6	9	0.021*	
	3	2.2	2.0	5.8	-10.2	11.2	0.4	4.5	9	0.391	
	4	4.5	5.3	5.8	-2.9	18.1	3.7	6.9	9	0.164	
MEAN	1	72.0	70.8	6.4	59.2	81.8	66.9	72.7	9	0.920	0.691
	2	68.7	71.1	11.6	49.2	85.8	67.6	80.7	9	0.479	
	3	75.8	69.1	14.2	48.4	85.0	60.8	80.7	9	0.140	
	4	73.3	75.1	5.4	69.9	86.9	71.1	77.2	9	0.094	
MEDIAN	1	70.3	70.2	6.3	59.1	79.6	67.1	74.3	9	0.971	0.534
	2	68.3	71.4	11.5	48.3	85.6	68.3	79.6	9	0.193	
	3	75.3	69.7	15.3	48.0	87.9	58.8	82.3	9	0.202	
	4	75.8	75.3	5.0	69.0	86.0	71.7	77.5	9	0.363	
MIN	1	63.8	62.6	5.2	52.8	70.3	60.8	66.0	9	0.873	0.744
	2	61.3	60.7	9.4	44.3	73.0	56.0	68.5	9	0.884	
	3	63.5	58.2	9.8	41.3	67.8	54.3	66.0	9	0.095	
	4	63.5	64.7	4.5	57.8	74.0	62.8	67.3	9	0.388	
MAX	1	82.4	84.8	11.0	70.5	110.0	81.5	86.0	9	0.089	0.811
	2	82.5	84.9	13.9	61.0	101.8	77.0	100.2	9	0.411	
	3	83.3	82.1	18.4	52.3	102.8	74.6	98.1	9	0.429	
	4	87.5	88.7	10.0	78.4	105.7	81.3	88.6	9	0.054	
Q1	1	67.4	66.9	6.5	55.4	75.5	63.1	69.6	9	0.836	0.958
	2	63.8	66.3	11.8	46.6	82.1	62.3	75.6	9	0.726	
	3	69.8	62.9	11.9	45.8	75.6	55.1	71.9	9	0.089	
	4	67.3	68.4	3.8	65.1	74.8	65.1	68.8	9	0.017*	
Q3	1	74.8	72.9	6.1	61.1	81.4	69.3	75.9	9	0.824	0.350
	2	73.3	74.4	11.7	50.9	89.7	69.7	81.8	9	0.387	
	3	81.0	74.4	16.6	49.2	92.3	64.8	87.6	9	0.131	
	4	79.0	80.6	7.1	72.0	95.4	75.5	83.9	9	0.478	

Table 11b

Summary Statistics and Tests for Summary Measures and Drug

After Data Replaced: Average 2 Hrs Systolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.2	-0.8	3.8	-10.3	2.9	-2.3	2.3	12	0.057	0.003*
	2	-3.8	-2.0	7.8	-11.4	19.9	-6.8	0.0	12	0.004*	
	3	-5.6	-7.6	6.7	-21.8	-0.5	-12.9	-3.4	11	0.100	
	4	-13.0	-13.3	11.1	-32.2	2.7	-19.9	-5.5	12	0.743	
MEAN	1	148.4	151.0	11.9	137.6	171.5	140.9	158.7	12	0.201	0.023*
	2	147.3	146.8	10.3	132.9	170.8	139.7	151.7	13	0.426	
	3	141.3	143.2	17.2	108.2	176.2	135.6	153.7	11	0.562	
	4	137.9	135.5	9.8	119.8	151.1	128.4	141.9	12	0.538	
MEDIAN	1	151.8	153.8	12.3	138.6	177.2	144.2	162.8	12	0.562	0.008*
	2	150.0	148.7	10.4	130.5	171.0	142.4	154.8	13	0.836	
	3	143.6	144.1	16.6	107.0	174.2	138.6	153.7	11	0.353	
	4	138.3	136.6	9.3	118.9	150.1	130.5	143.0	12	0.828	
MIN	1	126.0	129.1	10.8	116.8	154.8	121.4	134.9	12	0.106	0.165
	2	128.5	126.7	13.3	108.0	156.8	117.0	134.3	13	0.302	
	3	131.3	129.1	20.1	98.8	165.0	117.5	140.8	11	0.776	
	4	114.5	116.6	15.2	83.8	141.5	108.8	128.3	12	0.766	
MAX	1	163.0	165.7	12.3	151.1	186.6	157.5	173.6	12	0.116	0.064
	2	164.5	164.3	9.3	150.5	185.3	157.6	168.0	13	0.492	
	3	153.9	157.1	18.4	119.0	192.0	148.6	169.8	11	0.583	
	4	154.1	152.9	13.1	133.5	178.0	142.9	159.9	12	0.207	
Q1	1	142.1	143.8	11.7	128.1	161.9	135.3	152.8	12	0.246	0.034*
	2	140.0	138.7	12.1	120.3	165.4	129.7	143.1	13	0.419	
	3	135.5	137.0	18.1	105.3	171.6	123.1	148.4	11	0.978	
	4	128.9	128.1	10.2	112.8	144.3	118.4	136.2	12	0.728	
Q3	1	157.8	159.2	12.9	140.8	182.4	150.7	166.0	12	0.627	0.012*
	2	155.8	154.8	10.0	139.2	176.1	149.5	159.9	13	0.837	
	3	147.7	148.5	17.2	111.5	181.5	142.4	158.7	11	0.396	
	4	144.4	143.0	8.7	126.0	154.6	137.8	149.0	12	0.141	

Table 11b cont

After Data Replaced: Average 2 Hrs Systolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-6.8	-7.1	4.3	-14.8	-2.1	-9.6	-3.6	8	0.609	0.065
	2	-3.6	-3.4	5.4	-11.2	4.5	-7.4	-0.7	9	0.630	
	3	-6.6	-5.8	7.3	-15.7	10.0	-8.5	-5.2	9	0.252	
	4	-8.5	-11.2	5.6	-21.4	-6.5	-15.4	-7.0	9	0.026*	
MEAN	1	151.4	147.5	17.7	121.7	179.8	134.7	156.2	9	0.885	0.538
	2	143.2	145.6	12.1	122.3	162.6	140.9	154.0	9	0.793	
	3	147.2	148.2	11.6	129.2	168.7	140.9	151.0	9	0.935	
	4	143.6	138.4	11.8	119.5	151.1	131.3	148.0	9	0.298	
MEDIAN	1	153.6	150.9	16.6	122.2	177.7	140.0	159.5	9	0.977	0.330
	2	145.1	147.3	13.1	123.1	166.2	142.6	155.4	9	0.659	
	3	151.2	152.8	12.1	131.6	175.3	148.3	154.6	9	0.549	
	4	146.5	141.6	10.7	124.8	152.8	135.6	149.1	9	0.140	
MIN	1	117.0	124.1	22.2	94.3	172.0	110.8	132.5	9	0.342	0.258
	2	129.3	127.8	8.8	107.8	137.8	126.8	133.0	9	0.112	
	3	126.5	122.0	9.6	105.5	131.8	112.5	128.0	9	0.059	
	4	113.5	117.0	10.7	100.5	133.0	111.3	122.0	9	0.781	
MAX	1	162.9	164.3	21.8	127.1	191.3	152.0	180.0	9	0.799	0.570
	2	161.8	162.2	16.5	136.5	181.5	150.4	180.0	9	0.467	
	3	165.5	167.1	15.6	139.2	192.1	163.9	166.9	9	0.184	
	4	163.5	154.7	16.2	126.4	172.0	147.8	164.4	9	0.221	
Q1	1	138.4	139.0	17.0	119.1	173.3	124.3	145.1	9	0.346	0.491
	2	136.8	137.7	10.5	116.1	152.5	134.8	142.4	9	0.621	
	3	139.1	135.9	10.5	117.1	150.4	132.3	140.0	9	0.801	
	4	127.8	128.9	12.1	113.5	143.1	120.3	141.1	9	0.170	
Q3	1	161.8	156.5	18.9	123.3	186.9	145.3	165.6	9	0.943	0.301
	2	151.0	152.6	14.5	127.3	175.5	146.0	162.3	9	0.974	
	3	156.5	159.8	13.9	135.5	185.2	155.9	163.0	9	0.651	
	4	150.3	147.1	13.1	125.8	164.5	138.8	155.3	9	0.845	

Table 11c

Summary Statistics and Tests for Summary Measures and Drug

After Data Replaced: Average 2 Hrs Diastolic Blood Pressure: Centre 1

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-0.5	-1.4	4.7	-9.0	5.3	-5.1	2.4	12	0.388	0.002*
	2	-2.4	-0.9	5.8	-6.4	14.7	-4.5	0.8	12	0.006*	
	3	-8.0	-7.7	4.3	-13.0	0.4	-11.5	-5.3	11	0.596	
	4	-6.3	-7.8	6.2	-21.0	1.4	-11.6	-4.8	12	0.651	
MEAN	1	96.4	95.3	7.5	77.7	109.8	92.8	97.6	12	0.145	0.038*
	2	93.9	95.3	6.1	83.2	105.4	92.3	97.2	13	0.393	
	3	91.4	89.4	8.1	70.8	98.9	84.7	97.0	11	0.185	
	4	87.3	88.0	8.5	77.4	103.1	80.4	93.0	12	0.411	
MEDIAN	1	98.4	97.4	7.9	79.3	113.3	94.3	99.5	12	0.138	0.026*
	2	95.8	96.0	6.3	82.2	107.7	92.9	100.3	13	0.795	
	3	91.3	90.6	8.3	70.3	101.1	86.1	96.8	11	0.107	
	4	90.2	89.9	7.1	78.8	101.6	84.0	94.5	12	0.914	
MIN	1	78.5	77.9	7.5	66.5	94.8	72.9	81.0	12	0.346	0.701
	2	78.0	77.8	6.6	66.0	91.0	73.8	80.8	13	0.595	
	3	76.5	76.1	9.4	62.8	91.8	66.8	81.0	11	0.622	
	4	71.1	70.9	15.1	45.3	96.0	57.0	81.4	12	0.847	
MAX	1	109.7	108.7	8.6	87.5	120.1	106.4	113.4	12	0.134	0.004*
	2	112.6	112.6	8.3	100.4	128.5	106.4	115.8	13	0.587	
	3	105.3	101.3	9.3	80.3	112.2	93.1	106.3	11	0.077	
	4	97.7	100.9	8.2	91.5	116.1	94.6	106.7	12	0.188	
Q1	1	87.5	87.9	8.3	71.4	103.4	83.9	93.1	12	0.981	0.130
	2	87.1	88.1	7.3	70.4	98.4	86.1	91.8	13	0.258	
	3	84.6	83.7	8.1	66.4	93.5	79.6	91.5	11	0.229	
	4	81.5	81.9	8.5	72.2	98.4	74.4	86.6	12	0.259	
Q3	1	103.0	102.8	7.5	83.7	115.3	100.3	106.5	12	0.056	0.010*
	2	102.9	102.3	6.9	90.5	114.9	98.4	105.8	13	0.836	
	3	97.5	94.9	8.6	74.2	103.8	89.1	102.5	11	0.085	
	4	92.9	94.1	8.5	81.4	107.6	87.4	99.7	12	0.713	

Table 11c cont.

After Data Replaced: Average 2 Hrs Diastolic Blood Pressure: Centre 2

SM	DRUG	MEDIAN	MEAN	STD	MIN	MAX	Q1	Q3	N	NORMAL	K.W
CHANGE	1	-5.4	-6.4	3.3	-11.3	-3.0	-9.6	-3.7	8	0.213	0.036*
	2	-2.0	-2.2	3.1	-7.2	1.8	-3.4	-0.2	9	0.707	
	3	-7.3	-4.5	6.0	-9.4	9.8	-7.7	-3.1	9	0.009*	
	4	-6.9	-7.3	3.1	-13.6	-3.8	-9.2	-5.4	9	0.365	
MEAN	1	93.6	92.3	9.1	79.1	106.6	88.5	94.7	9	0.467	0.595
	2	93.4	92.3	6.6	84.0	100.8	87.4	98.1	9	0.283	
	3	88.3	90.4	8.2	81.2	102.5	83.7	94.5	9	0.185	
	4	89.2	88.1	6.4	78.4	99.1	84.8	91.7	9	0.663	
MEDIAN	1	95.5	94.5	8.4	79.3	106.2	91.9	97.7	9	0.739	0.762
	2	94.9	93.6	7.8	84.3	104.0	87.4	98.9	9	0.325	
	3	91.4	93.4	8.6	80.7	106.1	88.1	98.9	9	0.674	
	4	91.9	90.7	6.2	80.9	99.4	86.4	95.3	9	0.721	
MIN	1	74.3	75.3	13.4	53.0	100.3	67.8	83.3	9	0.883	0.229
	2	75.8	77.0	7.5	64.5	91.0	75.2	80.0	9	0.870	
	3	70.0	72.2	8.1	61.3	84.8	67.3	78.0	9	0.771	
	4	67.5	69.4	6.9	63.0	85.5	64.8	70.8	9	0.047*	
MAX	1	108.3	104.5	11.9	83.8	117.8	97.6	112.6	9	0.411	0.712
	2	104.5	104.9	7.8	94.3	114.5	97.1	110.3	9	0.349	
	3	101.3	102.4	8.2	90.3	115.5	97.6	107.3	9	0.908	
	4	103.1	100.7	8.0	86.5	111.3	96.4	104.6	9	0.836	
Q1	1	88.1	86.2	9.8	70.0	102.9	81.0	90.4	9	0.987	0.387
	2	83.3	86.0	7.6	77.7	96.0	80.9	95.1	9	0.059	
	3	84.6	83.1	8.7	68.3	95.8	78.4	85.7	9	0.868	
	4	78.4	80.3	6.4	72.6	92.6	76.5	83.4	9	0.652	
Q3	1	100.3	98.6	9.4	81.9	111.0	96.1	104.8	9	0.789	0.881
	2	100.7	98.0	7.1	89.9	107.7	91.5	102.7	9	0.117	
	3	95.9	97.8	8.6	86.3	112.1	91.8	102.6	9	0.856	
	4	96.6	95.4	7.4	84.0	105.3	91.7	100.9	9	0.788	

Table 12a

Frequencies and Chi Squared Tests for Abnormally 'High' Results at Each Time Point : Heart Rate (beats/min): Original Data ONLY.

Time	Treatment				p-value
	1 (N=21)	2 (N=22)	3 (N=22)	4 (N=21)	
	% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)	
Baseline	0 (0/20)	0 (0/21)	0 (0/22)	0 (0/21)	
1 Hr	0 (0/19)	0 (0/22)	0 (0/21)	0 (0/21)	
2 Hrs	0 (0/21)	0 (0/22)	0 (0/21)	0 (0/21)	
3 Hrs	4.8 (1/21)	0 (0/21)	9.5 (2/21)	0 (0/21)	0.611
4 Hrs	0 (0/21)	0 (0/22)	0 (0/22)	0 (0/21)	
5 Hrs	4.8 (1/21)	0 (0/22)	9.1 (2/22)	4.8 (1/21)	0.698
6 Hrs	0 (0/21)	0 (0/22)	4.5 (1/22)	0 (0/21)	1.000
7 Hrs	0 (0/21)	4.5 (1/22)	4.5 (1/22)	4.8 (1/21)	1.000
8 Hrs	4.8 (1/21)	13.6 (3/22)	9.1 (2/22)	4.8 (1/21)	0.829
9 Hrs	14.3 (3/21)	9.1 (2/22)	9.1 (2/22)	0 (0/21)	0.448
10 Hrs	4.8 (1/21)	0 (0/22)	0 (0/22)	0 (0/21)	0.488
11 Hrs	14.3 (3/21)	18.2 (4/22)	18.2 (4/22)	14.3 (3/21)	1.000
12 Hrs	19 (4/21)	22.7 (5/22)	13.6 (3/22)	0 (0/21)	0.119
13 Hrs	0 (0/20)	9.5 (2/21)	13.6 (3/22)	9.5 (2/21)	0.503
14 Hrs	0 (0/21)	4.5 (1/22)	9.5 (2/21)	0 (0/21)	0.464
15 Hrs	4.8 (1/21)	9.1 (2/22)	0 (0/22)	4.8 (1/21)	0.698
16 Hrs	0 (0/21)	4.5 (1/22)	0 (0/22)	0 (0/21)	1.000
17 Hrs	0 (0/21)	0 (0/22)	0 (0/22)	0 (0/21)	
18 Hrs	0 (0/20)	0 (0/22)	0 (0/20)	0 (0/21)	
19 Hrs	0 (0/20)	0 (0/22)	0 (0/20)	0 (0/21)	
20 Hrs	0 (0/21)	0 (0/22)	0 (0/20)	0 (0/21)	
21 Hrs	0 (0/21)	0 (0/22)	0 (0/21)	4.8 (1/21)	0.741
22 Hrs	4.8 (1/21)	9.1 (2/22)	4.8 (1/21)	5 (1/20)	1.000
23 Hrs	35 (7/20)	27.3 (6/22)	19 (4/21)	15.8 (3/19)	0.517
24 Hrs	4.8 (1/21)	0 (0/22)	4.5 (1/22)	14.3 (3/21)	0.231

Table 12b

Frequencies and Chi Squared Tests for Abnormally 'High' Results at Each Time Point
Systolic BP (mmHg): Original Data ONLY.

Time	Treatment				p-value
	1 (N=21)	2 (N=22)	3 (N=22)	4 (N=21)	
	% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)	
Baseline	80.0 (16/20)	85.7 (18/21)	86.4 (19/22)	66.7 (14/21)	0.376
1 Hr	78.9 (15/19)	81.8 (18/22)	81.0 (17/21)	52.4 (11/21)	0.091
2 Hrs	81.0 (17/21)	86.4 (19/22)	76.2 (16/21)	61.9 (13/21)	0.310
3 Hrs	85.7 (18/21)	85.7 (18/21)	85.7 (18/21)	71.4 (15/21)	0.624
4 Hrs	81.0 (17/21)	68.2 (15/22)	77.3 (17/22)	61.9 (13/21)	0.500
5 Hrs	85.7 (18/21)	86.4 (19/22)	90.9 (20/22)	71.4 (15/21)	0.426
6 Hrs	95.2 (20/21)	81.8 (18/22)	68.2 (15/22)	47.6 (10/21)	**0.004***
7 Hrs	85.7 (18/21)	90.9 (20/22)	81.8 (18/22)	61.9 (13/21)	0.120
8 Hrs	90.5 (19/21)	86.4 (19/22)	72.7 (16/22)	42.9 (9/21)	**0.002***
9 Hrs	85.7 (18/21)	72.7 (16/22)	72.7 (16/22)	61.9 (13/21)	0.384
10 Hrs	95.2 (20/21)	81.8 (18/22)	77.3 (17/22)	61.9 (13/21)	0.060
11 Hrs	85.7 (18/21)	77.3 (17/22)	86.4 (19/22)	66.7 (14/21)	0.393
12 Hrs	81.0 (17/21)	81.8 (18/22)	77.3 (17/22)	61.9 (13/21)	0.399
13 Hrs	75.0 (15/20)	85.7 (18/21)	68.2 (15/22)	57.1 (12/21)	0.218
14 Hrs	85.7 (18/21)	72.7 (16/22)	66.7 (14/21)	52.4 (11/21)	0.128
15 Hrs	61.9 (13/21)	77.3 (17/22)	45.5 (10/22)	52.4 (11/21)	0.160
16 Hrs	33.3 (7/21)	50.0 (11/22)	18.2 (4/22)	4.8 (1/21)	**0.006***
17 Hrs	42.9 (9/21)	22.7 (5/22)	27.3 (6/22)	9.5 (2/21)	0.099
18 Hrs	35.0 (7/20)	31.8 (7/22)	30.0 (6/20)	9.5 (2/21)	0.231
19 Hrs	20.0 (4/20)	13.6 (3/22)	25.0 (5/20)	4.8 (1/21)	0.304
20 Hrs	23.8 (5/21)	31.8 (7/22)	40.0 (8/20)	9.5 (2/21)	0.144
21 Hrs	28.6 (6/21)	13.6 (3/22)	28.6 (6/21)	14.3 (3/21)	0.442
22 Hrs	47.6 (10/21)	54.5 (12/22)	52.4 (11/21)	40.0 (8/20)	0.794
23 Hrs	80.0 (16/20)	81.8 (18/22)	76.2 (16/21)	42.1 (8/19)	**0.019***
24 Hrs	81.0 (17/21)	81.8 (18/22)	72.7 (16/22)	52.4 (11/21)	0.116

Table 12c

Frequencies and Chi Squared Tests for Abnormally 'High' Results at Each Time Point
Diastolic BP (mmHg): Original Data ONLY.

Time	Treatment				p-value
	1 (N=21)	2 (N=22)	3 (N=22)	4 (N=21)	
	% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)	
Baseline	85.0 (17/20)	76.2 (16/21)	86.4 (19/22)	71.4 (15/21)	0.607
1 Hr	84.2 (16/19)	81.8 (18/22)	81.0 (17/21)	81.0 (17/21)	1.000
2 Hrs	81.0 (17/21)	86.4 (19/22)	57.1 (12/21)	66.7 (14/21)	0.124
3 Hrs	81.0 (17/21)	81.0 (17/21)	66.7 (14/21)	57.1 (12/21)	0.241
4 Hrs	81.0 (17/21)	81.8 (18/22)	59.1 (13/22)	71.4 (15/21)	0.290
5 Hrs	85.7 (18/21)	90.9 (20/22)	81.8 (18/22)	81.0 (17/21)	0.811
6 Hrs	81.0 (17/21)	63.6 (14/22)	31.8 (7/22)	38.1 (8/21)	**0.004***
7 Hrs	81.0 (17/21)	90.9 (20/22)	68.2 (15/22)	61.9 (13/21)	0.116
8 Hrs	85.7 (18/21)	86.4 (19/22)	63.6 (14/22)	61.9 (13/21)	0.106
9 Hrs	85.7 (18/21)	77.3 (17/22)	72.7 (16/22)	76.2 (16/21)	0.798
10 Hrs	85.7 (18/21)	90.9 (20/22)	77.3 (17/22)	71.4 (15/21)	0.359
11 Hrs	85.7 (18/21)	86.4 (19/22)	72.7 (16/22)	66.7 (14/21)	0.344
12 Hrs	76.2 (16/21)	77.3 (17/22)	59.1 (13/22)	81.0 (17/21)	0.367
13 Hrs	70.0 (14/20)	76.2 (16/21)	54.5 (12/22)	61.9 (13/21)	0.470
14 Hrs	71.4 (15/21)	72.7 (16/22)	57.1 (12/21)	47.6 (10/21)	0.269
15 Hrs	52.4 (11/21)	63.6 (14/22)	31.8 (7/22)	38.1 (8/21)	0.145
16 Hrs	23.8 (5/21)	31.8 (7/22)	9.1 (2/22)	9.5 (2/21)	0.166
17 Hrs	28.6 (6/21)	22.7 (5/22)	27.3 (6/22)	9.5 (2/21)	0.423
18 Hrs	25.0 (5/20)	22.7 (5/22)	25.0 (5/20)	23.8 (5/21)	1.000
19 Hrs	10.0 (2/20)	22.7 (5/22)	20.0 (4/20)	9.5 (2/21)	0.555
20 Hrs	19.0 (4/21)	9.1 (2/22)	25.0 (5/20)	9.5 (2/21)	0.479
21 Hrs	14.3 (3/21)	18.2 (4/22)	23.8 (5/21)	14.3 (3/21)	0.877
22 Hrs	33.3 (7/21)	45.5 (10/22)	52.4 (11/21)	40.0 (8/20)	0.641
23 Hrs	75.0 (15/20)	86.4 (19/22)	71.4 (15/21)	68.4 (13/19)	0.533
24 Hrs	81.0 (17/21)	81.8 (18/22)	81.8 (18/22)	57.1 (12/21)	0.163

Table 13a
Summary Statistics and Kruskal-Wallis Tests on Frequency of Occurrence
Heart Rate (beats/min)

Overall

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	1.6+/-3.2	0-14	(N=21)	0.348
	Drug 2	3.8+/-5.6	0-23	(N=22)	
	Drug 3	4.0+/-7.2	0-24	(N=22)	
	Drug 4	1.1+/-2.5	0-10	(N=21)	
Normal	Drug 1	21+/-3.2	10-24	(N=21)	0.017*
	Drug 2	18.8+/-5.2	1-24	(N=22)	
	Drug 3	18.1+/-6.6	0-24	(N=22)	
	Drug 4	21.9+/-2.6	14-24	(N=21)	
High	Drug 1	1.1+/-1.7	0-6	(N=21)	0.748
	Drug 2	1.3+/-1.8	0-6	(N=22)	
	Drug 3	1.3+/-1.8	0-6	(N=22)	
	Drug 4	0.8+/-1.2	0-4	(N=21)	

Centre 1

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	1.1+/-1.6	0-4	(N=12)	0.660
	Drug 2	3.2+/-3.9	0-12	(N=13)	
	Drug 3	1.4+/-2.7	0-7	(N=12)	
	Drug 4	1.6+/-3	0-10	(N=12)	
Normal	Drug 1	20.8+/-2.1	17-24	(N=12)	0.338
	Drug 2	19.1+/-3.8	12-23	(N=13)	
	Drug 3	20.5+/-3.1	16-24	(N=12)	
	Drug 4	21.3+/-2.9	14-24	(N=12)	
High	Drug 1	1.8+/-1.9	0-6	(N=12)	0.664
	Drug 2	1.7+/-2.2	0-6	(N=13)	
	Drug 3	1.8+/-2.1	0-6	(N=12)	
	Drug 4	1+/-1.3	0-4	(N=12)	

Centre 2

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	2.2+/-4.5	0-14	(N=9)	0.316
	Drug 2	4.8+/-7.6	0-23	(N=9)	
	Drug 3	7.2+/-9.7	0-24	(N=10)	
	Drug 4	0.6+/-1.3	0-4	(N=9)	
Normal	Drug 1	21.2+/-4.4	10-24	(N=9)	0.031*
	Drug 2	18.3+/-7.1	1-24	(N=9)	
	Drug 3	15.2+/-8.6	0-23	(N=10)	
	Drug 4	22.7+/-2.1	19-24	(N=9)	
High	Drug 1	0.3+/-1	0-3	(N=9)	0.536
	Drug 2	0.8+/-1.1	0-3	(N=9)	
	Drug 3	0.7+/-1.1	0-3	(N=10)	
	Drug 4	0.6+/-1.1	0-3	(N=9)	

Table 13b

Summary Statistics and Kruskal-Wallis Tests on Frequency of Occurrence

Systolic BP (mmHg)

Overall

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0.1+/-0.7	0-3	(N=21)	0.619
	Drug 2	0+/-0.2	0-1	(N=22)	
	Drug 3	0.4+/-1.3	0-6	(N=22)	
	Drug 4	0.3+/-1	0-4	(N=21)	
Normal	Drug 1	7.3+/-5.6	0-24	(N=21)	0.016*
	Drug 2	8.0+/-5.7	0-24	(N=22)	
	Drug 3	8.4+/-5.6	0-19	(N=22)	
	Drug 4	12.9+/-6.5	3-24	(N=21)	
High	Drug 1	16.3+/-5.8	0-24	(N=21)	0.019*
	Drug 2	15.9+/-5.8	0-24	(N=22)	
	Drug 3	14.7+/-6.7	0-24	(N=22)	
	Drug 4	10.7+/-6.8	0-20	(N=21)	

Centre 1

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0+/-0	0-0	(N=12)	0.455
	Drug 2	0.1+/-0.3	0-1	(N=13)	
	Drug 3	0.7+/-1.8	0-6	(N=12)	
	Drug 4	0.4+/-1.2	0-4	(N=12)	
Normal	Drug 1	6.1+/-4.1	1-13	(N=12)	0.023*
	Drug 2	7.3+/-5.1	0-17	(N=13)	
	Drug 3	8.1+/-6.5	0-18	(N=12)	
	Drug 4	13.5+/-6.2	3-24	(N=12)	
High	Drug 1	17.6+/-4.1	11-23	(N=12)	0.026*
	Drug 2	16.5+/-5.1	7-24	(N=13)	
	Drug 3	14.9+/-7.3	0-24	(N=12)	
	Drug 4	10+/-6.5	0-20	(N=12)	

Centre 2

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0.3+/-1	0-3	(N=9)	0.537
	Drug 2	0+/-0	0-0	(N=9)	
	Drug 3	0+/-0	0-0	(N=10)	
	Drug 4	0.2+/-0.7	0-2	(N=9)	
Normal	Drug 1	8.9+/-7.2	0-24	(N=9)	0.695
	Drug 2	8.9+/-6.8	2-24	(N=9)	
	Drug 3	8.7+/-4.5	5-19	(N=10)	
	Drug 4	12+/-7.2	4-23	(N=9)	
High	Drug 1	14.6+/-7.4	0-24	(N=9)	0.688
	Drug 2	15+/-6.8	0-22	(N=9)	
	Drug 3	14.4+/-6.2	2-19	(N=10)	
	Drug 4	11.6+/-7.4	0-20	(N=9)	

Table 13c

Summary Statistics and Kruskal-Wallis Tests on Frequency of Occurrence
Diastolic BP (mmHg)

Overall

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0.2+/-0.9	0-4	(N=21)	0.025*
	Drug 2	0+/-0	0-0	(N=22)	
	Drug 3	0.3+/-0.9	0-4	(N=22)	
	Drug 4	0.6+/-1.2	0-4	(N=21)	
Normal	Drug 1	8.7+/-6	0-24	(N=21)	0.117
	Drug 2	8.5+/-4.8	1-19	(N=22)	
	Drug 3	10.6+/-5.2	3-20	(N=22)	
	Drug 4	11.3+/-5.6	0-21	(N=21)	
High	Drug 1	14.8+/-6.3	0-24	(N=21)	0.096
	Drug 2	15.4+/-4.7	5-23	(N=22)	
	Drug 3	12.5+/-6	1-21	(N=22)	
	Drug 4	12+/-6.2	2-23	(N=21)	

Centre 1

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0+/-0	0-0	(N=12)	0.034*
	Drug 2	0+/-0	0-0	(N=13)	
	Drug 3	0.5+/-1.2	0-4	(N=12)	
	Drug 4	0.8+/-1.4	0-4	(N=12)	
Normal	Drug 1	8.1+/-5.1	2-23	(N=12)	0.204
	Drug 2	7.4+/-3.7	1-16	(N=13)	
	Drug 3	10.3+/-5.1	4-19	(N=12)	
	Drug 4	11.3+/-5.9	0-20	(N=12)	
High	Drug 1	15.6+/-5	1-22	(N=12)	0.131
	Drug 2	16.5+/-3.7	8-23	(N=13)	
	Drug 3	12.9+/-5.6	1-19	(N=12)	
	Drug 4	11.8+/-6.5	3-23	(N=12)	

Centre 2

Frequency	DRUG	Mean+/-SD	RANGE	N	K.W.PROB
Low	Drug 1	0.4+/-1.3	0-4	(N=9)	0.531
	Drug 2	0+/-0	0-0	(N=9)	
	Drug 3	0.1+/-0.3	0-1	(N=10)	
	Drug 4	0.3+/-0.7	0-2	(N=9)	
Normal	Drug 1	9.6+/-7.2	0-24	(N=9)	0.769
	Drug 2	10.1+/-5.9	2-19	(N=9)	
	Drug 3	11.1+/-5.6	3-20	(N=10)	
	Drug 4	11.3+/-5.5	4-21	(N=9)	
High	Drug 1	13.8+/-7.9	0-24	(N=9)	0.838
	Drug 2	13.8+/-5.8	5-21	(N=9)	
	Drug 3	11.9+/-6.7	1-21	(N=10)	
	Drug 4	12.1+/-6.2	2-20	(N=9)	

Table 14a
Number of Abnormally High Results over the Course of the Study by Treatment: Heart Rate (N=86).

Number of Abnormally High Readings	Treatment				Total
	1	2	3	4	
0	11	10	10	13	44
1	4	6	6	3	19
2	3	2	2	2	9
3	1	1	1	2	5
4	-	-	1	1	2
5	1	2	1	-	4
6	1	1	1	-	3

Table 14b

Number of Abnormally High Results over the Course of the Study by Treatment: SBP (N=86).

Number of Abnormally High Readings	Treatment				Total
	1	2	3	4	
0	1	1	1	2	5
1	-	-	-	3	3
2	-	-	1	-	1
4	-	-	1	-	1
6	-	-	1	-	1
7	1	1	-	1	3
9	-	1	-	1	2
10	-	-	-	3	3
11	2	1	1	1	5
12	1	2	1	1	5
13	1	1	2	1	5
14	1	1	-	-	2
15	-	1	1	-	2
16	2	1	3	3	9
17	1	1	2	3	7
18	-	2	1	-	3
19	5	2	3	-	10
20	1	2	1	2	6
21	3	2	-	-	5
22	-	2	-	-	2
23	1	-	2	-	3
24	1	1	1	-	3

Table 14c

Number of Abnormally High Results over the Course of the Study by Treatment: DBP (N=86).

Number of Abnormally High Readings	Treatment				Total
	1	2	3	4	
0	1	-	-	-	1
1	1	-	2	-	3
2	1	-	-	2	3
3	-	-	-	1	1
4	-	-	1	1	2
5	-	1	-	-	1
6	-	-	1	1	2
7	-	-	1	1	2
8	-	2	1	1	4
9	-	1	-	-	1
10	-	-	2	1	3
11	-	1	-	1	2
12	-	1	3	-	4
13	-	-	1	1	2
14	1	-	1	1	3
15	5	1	-	6	12
16	4	6	1	-	11
17	2	2	2	-	6
18	2	1	2	-	5
19	1	2	3	2	8
20	1	1	-	1	3
21	-	2	1	-	3
22	1	-	-	-	1
23	-	1	-	1	2
24	1	-	-	-	1

Table 15a

Chi-squared Tests on Frequency of Occurrence of Abnormal Results by Treatment

Heart Rate (beats/min)

Centre	Number of Abnormal Readings	Treatment				P-Value
		1	2	3	4	
1	0	3	5	4	6	0.851
	0-3	7	5	5	5	
	4-6	2	3	3	1	
2	0	8	5	6	7	0.421
	0-3	1	4	4	2	
Overall	0	11	10	10	13	0.930
	0-3	8	9	9	7	
	4-6	2	3	3	1	

Table 15b

Chi-squared Tests on Frequency of Occurrence of Abnormal Results by Treatment

Systolic BP (mmHg)

Centre	Number of Abnormal Readings	Treatment				p-value
		1	2	3	4	
1	0-12	2	3	4	8	0.143
	13-18	3	5	4	3	
	19-24	7	5	4	1	
2	0-12	3	3	2	4	0.622
	13-18	2	2	5	4	
	19-24	4	4	3	1	
Overall	0-12	5	6	6	12	0.069
	13-18	5	7	9	7	
	19-24	11	9	7	2	

Table 15c

Chi-squared Tests on Frequency of Occurrence of Abnormal Results by Treatment

Diastolic BP (mmHg)

Centre	Number of Abnormal Readings	Treatment				P-value
		1	2	3	4	
1	0-12	1	2	5	6	0.179
	13-18	9	8	5	3	
	19-24	2	3	2	3	
2	0-12	2	4	6	3	0.502
	13-18	5	2	2	5	
	19-24	2	3	2	1	
Overall	0-12	3	6	11	9	0.195
	13-18	14	10	7	8	
	19-24	4	6	4	4	

Table 16b
Frequencies and Chi Squared Tests for Abnormally High Results
Systolic BP (mmHg)

Centre	Frequency of Occurrence	Treatment				P-value
		1 (N=21)	2 (N=22)	3 (N=22)	4 (N=21)	
		% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)	
1	>50% High	83.3 (10/12)	76.9 (10/13)	66.7 (8/12)	33.3 (4/12)	0.048*
	>75% High	58.3 (7/12)	38.5 (5/13)	33.3 (4/12)	8.3 (1/12)	0.081
2	>50% High	66.7 (6/9)	66.7 (6/9)	80 (8/10)	55.6 (5/9)	0.728
	>75% High	44.4 (4/9)	44.4 (4/9)	30 (3/10)	11.1 (1/9)	0.380
Overall	>50% High	76.2 (16/21)	72.7 (16/22)	72.7 (16/22)	42.9 (9/21)	0.075
	>75% High	52.4 (11/21)	40.9 (9/22)	31.8 (7/22)	9.5 (2/21)	0.025*

Table 16c
Frequencies and Chi Squared Tests for Abnormally High Results
Diastolic BP (mmHg)

Centre	Frequency of Occurrence	Treatment				P-value
		1 (N=21)	2 (N=22)	3 (N=22)	4 (N=21)	
		% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)	
1	>50% High	91.7 (11/12)	84.6 (11/13)	58.3 (7/12)	50 (6/12)	0.080
	>75% High	16.7 (2/12)	23.1 (3/13)	16.7 (2/12)	25 (3/12)	1.000
2	>50% High	77.8 (7/9)	55.6 (5/9)	40 (4/10)	66.7 (6/9)	0.424
	>75% High	22.2 (2/9)	33.3 (3/9)	20 (2/10)	11.1 (1/9)	0.827
Overall	>50% High	85.7 (18/21)	72.7 (16/22)	50 (11/22)	57.1 (12/21)	0.062
	>75% High	19 (4/21)	27.3 (6/22)	18.2 (4/22)	19 (4/21)	0.908

Table 17b

Logistic Regression Analysis on For more than 50% Abnormality after Adjusting for Centre.

Systolic BP (mmHg)

Analysis of Maximum Likelihood Estimates

Logistic Regression Analysis on the Full Model.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	0.2231	0.6708	0.1107	0.7394	.	.
ICENTRE	1	-0.9163	0.9083	1.0177	0.3131	-0.251585	0.400
IA	1	0.4700	0.9747	0.2325	0.6297	0.111975	1.600
IB	1	0.4700	0.9747	0.2325	0.6297	0.113725	1.600
IC	1	1.1632	1.0368	1.2585	0.2619	0.281442	3.200
INTA	1	1.8326	1.3874	1.7446	0.1866	0.352145	6.250
INTB	1	1.4271	1.3260	1.1583	0.2818	0.283494	4.167
INTC	1	0.2231	1.3509	0.0273	0.8688	0.042879	1.250

Logistic Regression Analysis on the Reduced Model adjusting for Centre.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.2260	0.5191	0.1896	0.6633	.	.
ICENTRE	1	-0.1083	0.4819	0.0505	0.8222	-0.029729	0.897
IA	1	1.4518	0.6762	4.6091	0.0318	0.345877	4.271
IB	1	1.2715	0.6513	3.8114	0.0509	0.307651	3.566
IC	1	1.2666	0.6511	3.7843	0.0517	0.306464	3.549

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
ICENTRE	1.0000	0.897	0.349	2.308
IA	1.0000	4.271	1.135	16.074
IB	1.0000	3.566	0.995	12.781
IC	1.0000	3.549	0.991	12.713

Table 17c

Logistic Regression Analysis For more than 50% Abnormality after Adjuting for Centre.

Diastolic BP (mmHg)

Analysis of Maximum Likelihood Estimates

Logistic Regression Analysis on the Full Model.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	0.6931	0.7071	0.9609	0.3270	.	.
ICENTRE	1	-0.6931	0.9129	0.5765	0.4477	-0.190316	0.500
IA	1	0.5596	1.0690	0.2740	0.6006	0.133324	1.750
IB	1	-0.4700	0.9747	0.2325	0.6297	-0.113725	0.625
IC	1	-1.0986	0.9574	1.3167	0.2512	-0.265826	0.333
INTA	1	1.8383	1.6022	1.3164	0.2512	0.353240	6.286
INTB	1	2.1748	1.3690	2.5234	0.1122	0.432011	8.800
INTC	1	1.4351	1.2621	1.2929	0.2555	0.275763	4.200

Logistic Regression Analysis on the Reduced Model adjusting for Centre.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-0.0253	0.5194	0.0024	0.9611	.	.
ICENTRE	1	0.5564	0.4829	1.3280	0.2492	0.152779	1.744
IA	1	1.5264	0.7696	3.9337	0.0473	0.363643	4.601
IB	1	0.6941	0.6565	1.1180	0.2903	0.167957	2.002
IC	1	-0.2785	0.6192	0.2023	0.6529	-0.067393	0.757

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
ICENTRE	1.0000	1.744	0.677	4.494
IA	1.0000	4.601	1.018	20.795
IB	1.0000	2.002	0.553	7.248
IC	1.0000	0.757	0.225	2.548

Table 18b

Logistic Regression Analysis For more than 75% Abnormality after Adjusting for Centre. Systolic BP (mmHg)

Analysis of Maximum Likelihood Estimates
Logistic Regression Analysis on the Full Model.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-2.0794	1.0607	3.8436	0.0499	.	.
ICENTRE	1	-0.3185	1.4886	0.0458	0.8306	-0.087437	0.727
IA	1	1.8563	1.2550	2.1878	0.1391	0.442248	6.400
IB	1	1.8563	1.2550	2.1878	0.1391	0.449160	6.400
IC	1	1.2321	1.2654	0.9482	0.3302	0.298136	3.429
INTA	1	0.8781	1.7346	0.2563	0.6127	0.168728	2.406
INTB	1	0.0716	1.7294	0.0017	0.9670	0.014222	1.074
INTC	1	0.4726	1.7513	0.0728	0.7873	0.090815	1.604

Logistic Regression Analysis on the Reduced Model adjusting for Centre.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-2.3117	0.7979	8.3946	0.0038	.	.
ICENTRE	1	0.1039	0.4892	0.0451	0.8318	0.028529	1.109
IA	1	2.3477	0.8625	7.4094	0.0065	0.559328	10.462
IB	1	1.8824	0.8608	4.7824	0.0288	0.455468	6.569
IC	1	1.4924	0.8733	2.9202	0.0875	0.361116	4.448

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
ICENTRE	1.0000	1.109	0.425	2.894
IA	1.0000	10.462	1.930	56.724
IB	1.0000	6.569	1.216	35.496
IC	1.0000	4.448	0.803	24.635

Table 18c

Logistic Regression Analysis For more than 75% Abnormality after Adjusting for Centre. Diastolic BP (mmHg)

Analysis of Maximum Likelihood Estimates
Logistic Regression Analysis on the Full Model.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-2.0794	1.0606	3.8437	0.0499	.	.
ICENTRE	1	0.9808	1.2528	0.6130	0.4337	0.269305	2.667
IA	1	0.8267	1.3296	0.3866	0.5341	0.196950	2.286
IB	1	1.3863	1.2747	1.1827	0.2768	0.335435	4.000
IC	1	0.6931	1.3229	0.2745	0.6003	0.167718	2.000
INTA	1	-1.3375	1.6770	0.6361	0.4251	-0.257012	0.263
INTB	1	-1.4917	1.5820	0.8890	0.3457	-0.296315	0.225
INTC	1	-1.2040	1.6717	0.5187	0.4714	-0.231353	0.300

Logistic Regression Analysis on the Reduced Model adjusting for Centre.

Variable	DF	Parameter Estimate	Standard Error	Wald Chi-Square	Pr > Chi-Square	Standardized Estimate	Odds Ratio
INTERCPT	1	-1.3982	0.6314	4.9036	0.0268	.	.
ICENTRE	1	-0.0863	0.5366	0.0258	0.8723	-0.023683	0.917
IA	1	-118E-18	0.7860	0.0000	1.0000	-2.81711E-17	1.000
IB	1	0.4679	0.7337	0.4067	0.5236	0.113222	1.597
IC	1	-0.0594	0.7841	0.0057	0.9396	-0.014378	0.942

Conditional Odds Ratios and 95% Confidence Intervals

Variable	Unit	Odds Ratio	Wald Confidence Limits Lower	Upper
ICENTRE	1.0000	0.917	0.320	2.626
IA	1.0000	1.000	0.214	4.667
IB	1.0000	1.597	0.379	6.726
IC	1.0000	0.942	0.203	4.381

Table 19a: Cumulative Survival estimates using Kaplan Meier Estimates for Time to an Abnormally High Result.: Heart Rate (beats/minute)

Time On Study (Hours)	TREATMENT															
	1				2				3				4			
	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E
0	21	0	0	-	22	0	0	-	22	0	0	-	21	0	0	-
3	20	1	4.8	4.7					20	2	9.1	6.1				
5	19	2	9.5	6.4					18	4	18.2	8.2	20	1	4.8	4.7
6									17	5	22.7	8.9				
7					21	1	4.6	4.4								
8	18	3	14.3	7.6	19	3	13.6	7.3	15	7	31.8	9.9	19	2	9.5	6.4
9	16	5	23.8	9.3					14	8	36.4	10.3				
11	14	7	33.3	10.3	17	5	22.7	8.9	13	9	40.9	10.5	16	5	23.8	9.3
12	12	9	42.9	10.8	14	8	36.4	10.3								
13					13	9	40.9	10.5	12	10	45.5	10.6				
21													15	6	28.6	9.9
22					12	10	45.5	10.6								
23	11	10	47.6	10.9	10	12	54.6	10.6	10	12	54.6	10.6	14	7	33.3	10.3
24 ©	0	10 ©	47.6	10.9	0	12 ©	54.6	10.6	0	12 ©	54.6	10.6	0	8 ©	38.1	10.6

Log-Rank p-value=0.590, Wilcoxon p-value=0.470

Note: © : shows censored observations i.e. Individuals that had no abnormalities and were censored at time 24 hours. R= Number of individuals at risk at that time on study. NE= Number of individuals with an event at that time.%= Percentage of those remaining that failed. S.E. = Standard Error of the percentage.

Table 19b: Cumulative Survival estimates using Kaplan Meier Estimates for Time to an Abnormally High Result. Systolic Blood Pressure (mmHg)

Time On Study (Hours)	TREATMENT															
	1				2				3				4			
	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E
0	21	0	0	-	22	0	0	-	22	0	0	-	21	0	0	-
1	6	15	71.4	9.9	4	18	81.8	8.2	5	17	77.3	8.9	10	11	52.4	10.9
2	4	17	81.0	8.6	2	20	90.9	6.1	3	19	86.4	7.3	8	13	61.9	10.6
3	2	19	90.5	6.4	1	21	95.5	4.4					6	15	71.4	9.9
4									2	20	90.9	6.1	5	16	76.2	9.3
5	1	20	95.2	4.7												
11									1	21	95.5	4.4	4	17	81.0	8.6
13													3	18	85.7	7.6
15													2	19	90.5	6.4
24 ©	0	20 ©	95.2	0.47	0	21 ©	95.4	4.4	0	21 ©	95.2	4.4	0	19 ©	90.5	6.4

Log-Rank p-value=0.263, Wilcoxon p-value=0.116

Note: © : shows censored observations i.e. Individuals that had no abnormalities and were censored at time 24 hours.
NR= Number of individuals at risk at that time on study. NE= Number of individuals with an event at that time.
%= Percentage of those remaining that failed. S.E. = Standard Error of the percentage.

Table 19c: Cumulative Survival estimates using Kaplan Meier Estimates for Time to an Abnormally High Result.: Diastolic Blood Pressure (mmHg)

Time On Study (Hours)	TREATMENT															
	1				2				3				4			
	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E	NR	NE	%	S.E
0	21	0	0	-	22	0	0	-	22	0	0	-	21	0	0	-
1	5	16	76.2	9.3	4	18	81.8	8.2	5	17	77.3	8.9	4	17	81.0	8.6
2	3	18	85.7	7.6	2	20	90.9	6.1								
4									3	19	86.4	7.3	2	19	90.5	6.4
5					1	21	95.5	4.4								
8					0	22	100.0	-								
9	2	19	90.5	6.4					2	20	90.9	6.1	1	20	95.2	4.7
13													0	21	100.0	-
16	1	20	95.2	4.7												
21									1	21	95.5	4.4				
24	0	20 ©	95.2	4.7					0	22	100.0	-				

Log-Rank p-value=0.412, Wilcoxon p-value=0.919

Note: © : shows censored observations i.e. Individuals that had no abnormalities and were censored at time 24 hours.
NR= Number of individuals at risk at that time on study. NE= Number of individuals with an event at that time.
%= Percentage of those remaining that failed. S.E. = Standard Error of the percentage.

Table 20a
Final Selected Mixed Models for
Heart Rate Data (b/m)

Original Data: Adjust for Time and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	10569.422527	
1	2	10321.156006	0.00000000

Convergence criteria met.

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
CS	PATIENT	15.93802351
Residual		67.20719991

Model Fitting Information for VALUE

Description	Value
Observations	1992.000
Res Log Likelihood	-6901.97
Akaike's Information Criterion	-6903.97
Schwarz's Bayesian Criterion	-6909.51
-2 Res Log Likelihood	13803.93
Null Model LRT Chi-Square	248.2665
Null Model LRT DF	1.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	79	294.80	0.0001
TIME	23	1816	46.92	0.0001
DRUG	3	79	1.32	0.2723
TIME*DRUG	69	1816	1.00	0.4866

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	79	0.02	0.8886
G 1 vs G3	1	79	0.11	0.7430
G 1 vs G4	1	79	2.03	0.1582
G 2 vs G3	1	79	0.04	0.8501
G 2 vs G4	1	79	2.51	0.1170
G 3 vs G4	1	79	3.22	0.0767

Method 1: Adjust for Time, Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	3201.8344723	
1	2	2946.1671936	0.00000046
2	1	2946.1665083	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	656.0000
Res Log Likelihood	-2045.58
Akaike's Information Criterion	-2081.58
Schwarz's Bayesian Criterion	-2161.40
-2 Res Log Likelihood	4091.164
Null Model LRT Chi-Square	255.6680
Null Model LRT DF	35.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	274.34	0.0001
TIME	7	77	50.33	0.0001
DRUG	3	77	1.14	0.3379
TIME*DRUG	21	77	1.37	0.1588

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	0.02	0.8936
G 1 vs G3	1	77	0.08	0.7801
G 1 vs G4	1	77	1.80	0.1840
G 2 vs G3	1	77	0.02	0.8816
G 2 vs G4	1	77	2.23	0.1396
G 3 vs G4	1	77	2.65	0.1078

Method 2: Adjust for Time, and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	4961.8472792	
1	2	4505.8940051	0.00000023
2	1	4505.8934880	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	984.0000
Res Log Likelihood	-3112.15
Akaike's Information Criterion	-3190.15
Schwarz's Bayesian Criterion	-3378.94
-2 Res Log Likelihood	6224.309
Null Model LRT Chi-Square	455.9538
Null Model LRT DF	77.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	304.35	0.0001
TIME	11	77	34.95	0.0001
DRUG	3	77	1.15	0.3332
TIME*DRUG	33	77	1.10	0.3592

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	0.02	0.8932
G 1 vs G3	1	77	0.07	0.7858
G 1 vs G4	1	77	1.83	0.1804
G 2 vs G3	1	77	0.02	0.8879
G 2 vs G4	1	77	2.26	0.1365
G 3 vs G4	1	77	2.66	0.1071

Table 20b
Final Selected Mixed Models for
Systolic BP (mmHg)

Original Data: Adjust for Time and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	11594.616898	
1	2	11143.166845	0.00000000

Convergence criteria met.

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
CS	PATIENT	40.87530639
Residual		101.69061144

Model Fitting Information for VALUE

Description	Value
Observations	1992.000
Res Log Likelihood	-7312.97
Akaike's Information Criterion	-7314.97
Schwarz's Bayesian Criterion	-7320.52
-2 Res Log Likelihood	14625.94
Null Model LRT Chi-Square	451.4501
Null Model LRT DF	1.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	79	192.45	0.0001
TIME	23	1816	66.42	0.0001
DRUG	3	79	9.41	0.0001
TIME*DRUG	69	1816	0.88	0.7475

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	79	0.02	0.9015
G 1 vs G3	1	79	2.82	0.0968
G 1 vs G4	1	79	20.13	0.0001
G 2 vs G3	1	79	3.32	0.0724
G 2 vs G4	1	79	21.89	0.0001
G 3 vs G4	1	79	8.34	0.0050

Method 1: Adjust for Time, Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	3578.9605278	
1	2	3233.5174799	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	656.0000
Res Log Likelihood	-2189.26
Akaike's Information Criterion	-2225.26
Schwarz's Bayesian Criterion	-2305.08
-2 Res Log Likelihood	4378.515
Null Model LRT Chi-Square	345.4430
Null Model LRT DF	35.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	209.57	0.0001
TIME	7	77	49.29	0.0001
DRUG	3	77	9.18	0.0001
TIME*DRUG	21	77	0.99	0.4894

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	0.02	0.8889
G 1 vs G3	1	77	2.36	0.1288
G 1 vs G4	1	77	19.58	0.0001
G 2 vs G3	1	77	2.85	0.0956
G 2 vs G4	1	77	21.44	0.0001
G 3 vs G4	1	77	8.23	0.0053

Method 2: Adjust for Time, and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	5488.0354094	
1	2	4934.9030469	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	984.0000
Res Log Likelihood	-3326.66
Akaike's Information Criterion	-3404.66
Schwarz's Bayesian Criterion	-3593.44
-2 Res Log Likelihood	6653.318
Null Model LRT Chi-Square	553.1324
Null Model LRT DF	77.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	211.49	0.0001
TIME	11	77	33.08	0.0001
DRUG	3	77	9.21	0.0001
TIME*DRUG	33	77	1.13	0.3199

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	0.01	0.9031
G 1 vs G3	1	77	2.34	0.1301
G 1 vs G4	1	77	19.75	0.0001
G 2 vs G3	1	77	2.77	0.1001
G 2 vs G4	1	77	21.45	0.0001
G 3 vs G4	1	77	8.37	0.0050

Table 20c
Final Selected Mixed Models for
Diastolic BP (mmHg)

Original Data: Adjust for Time and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	10621.690802	
1	2	10303.057354	0.00000000

Convergence criteria met.

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
CS	PATIENT	19.20695240
Residual		66.10349926

Model Fitting Information for VALUE

Description	Value
Observations	1992.000
Res Log Likelihood	-6892.92
Akaike's Information Criterion	-6894.92
Schwarz's Bayesian Criterion	-6900.46
-2 Res Log Likelihood	13785.83
Null Model LRT Chi-Square	318.6334
Null Model LRT DF	1.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	79	121.51	0.0001
TIME	23	1816	72.16	0.0001
DRUG	3	79	7.13	0.0003
TIME*DRUG	69	1816	1.16	0.1748

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	79	1.17	0.2831
G 1 vs G3	1	79	4.14	0.0452
G 1 vs G4	1	79	9.05	0.0035
G 2 vs G3	1	79	10.03	0.0022
G 2 vs G4	1	79	17.22	0.0001
G 3 vs G4	1	79	1.05	0.3096

Method 1: Adjust for Time, Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	3186.3017083	
1	2	2929.7106451	0.00000005
2	1	2929.7105753	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	656.0000
Res Log Likelihood	-2037.35
Akaike's Information Criterion	-2073.35
Schwarz's Bayesian Criterion	-2153.18
-2 Res Log Likelihood	4074.708
Null Model LRT Chi-Square	256.5911
Null Model LRT DF	35.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	141.32	0.0001
TIME	7	77	78.64	0.0001
DRUG	3	77	6.98	0.0003
TIME*DRUG	21	77	1.16	0.3122

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	1.31	0.2562
G 1 vs G3	1	77	3.82	0.0543
G 1 vs G4	1	77	8.59	0.0044
G 2 vs G3	1	77	9.75	0.0025
G 2 vs G4	1	77	17.08	0.0001
G 3 vs G4	1	77	0.92	0.3417

Method 2: Adjust for Time, and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	4947.1878936	
1	2	4562.7211667	0.00000001
2	1	4562.7211409	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	984.0000
Res Log Likelihood	-3140.57
Akaike's Information Criterion	-3218.57
Schwarz's Bayesian Criterion	-3407.35
-2 Res Log Likelihood	6281.136
Null Model LRT Chi-Square	384.4668
Null Model LRT DF	77.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	77	140.26	0.0001
TIME	11	77	53.58	0.0001
DRUG	3	77	6.99	0.0003
TIME*DRUG	33	77	1.38	0.1249

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	77	1.26	0.2646
G 1 vs G3	1	77	3.87	0.0529
G 1 vs G4	1	77	8.71	0.0042
G 2 vs G3	1	77	9.71	0.0026
G 2 vs G4	1	77	17.08	0.0001
G 3 vs G4	1	77	0.93	0.3378

Table 20d
Final Selected Mixed Models for
Dietary Response Data

Original Data Adjust for Time and Base

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	-605.7076663	
1	2	-632.7527163	0.00000006
2	1	-632.7527339	0.00000000

Convergence criteria met.

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
CS	SUBJECT	0.00269038
Residual		0.00728640

Model Fitting Information for RESPONSE

Description	Value
Observations	211.0000
Res Log Likelihood	148.2106
Akaike's Information Criterion	146.2106
Schwarz's Bayesian Criterion	143.0011
-2 Res Log Likelihood	-296.421
Null Model LRT Chi-Square	27.0451
Null Model LRT DF	1.0000
Null Model LRT P-Value	0.0000

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
BASE	1	20	2.62	0.1214
TIME	8	163	7.00	0.0001
GROUP	2	20	63.92	0.0001
TIME*GROUP	16	163	7.94	0.0001

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	20	29.52	0.0001
G 1 vs G3	1	20	127.68	0.0001
G 2 vs G3	1	20	36.28	0.0001

Method 1: Adjust for Base and Time

REML Estimation Iteration History

Iteration	Evaluations	Objective	Criterion
0	1	-224.4049275	
1	2	-250.8973360	0.00000039
2	1	-250.8973855	0.00000000

Convergence criteria met.

Model Fitting Information for VALUE

Description	Value
Observations	66.0000
Res Log Likelihood	73.9881
Akaike's Information Criterion	67.9881
Schwarz's Bayesian Criterion	61.9121
-2 Res Log Likelihood	-147.976
Null Model LRT Chi-Square	26.4925
Null Model LRT DF	5.0000
Null Model LRT P-Value	0.0001

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
TIME	2	18	2.61	0.1010
BASE	1	18	4.18	0.0559
GROUP	2	18	58.78	0.0001
TIME*GROUP	4	18	41.39	0.0001

CONTRAST Statement Results

Source	NDF	DDF	F	Pr > F
G 1 vs G2	1	18	29.81	0.0001
G 1 vs G3	1	18	117.49	0.0001
G 2 vs G3	1	18	27.87	0.0001

APPENDIX B

```
/*************************************************************************************************
Program Name: ORIGDATA.SAS
Date:         Jan-15-96
Programmer:   Sharayu Shanbhag

Description: Selects out required data for original ambulatory and diet data sets.
input: ABP.ABPMDIF (For Data set A)
       DIET.DIET (for Data set B)
output: ABP.OUNI_1 (contains CENTRE (1-2), TIME (0-24),PATIENT, MEASURE (SBP,HR,DBP),
                            VALUE, DRUG (1-4),BASE).
        ABP.OMULT_1 (contains CENTRE, PATIENT, MEASURE, DRUG, BASE, _1 to _24).
        DIET.OUNI_1 (contains TIME (0-9),SUBJECT, RESPONSE, GROUP (1-3),BASE).
        DIET.OMULT_1 (contains SUBJECT, RESPONSE, GROUP, BASE, _1 to _9).
*************************************************************************************************/
options pageno=1 ls=65 ps=55 nodate;
libname abp  '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
%macro data(l,in,perm,vars,sort,t,v,b,multt,title,set);
**********************************;
 ** DATA SET IN UNIVARIATE FORM **;
 ** CONTAINED SOME MISSING RECORDS *;
 ** Set Base for data set B and **;
 **     Time=0 for data set A **;
**********************************;
   data origuni(keep=&vars);
        set &perm..&in;
   run;
   %if &l=1 %then %do;
   data base;
        set origuni(keep=patient base measure centre drug);
        time=0;
        value=base;
   run;
   proc sort data=base nodupkey;
        by patient measure;
   run;
   data origuni;
        set origuni
            base;
   run;
   %end;
   %if &l=2 %then %do;
   data base(keep=subject base);
        set origuni;
        base=&v;
        if time=0 then output;
   run;
   proc sort data=base nodupkey;
        by subject;
   run;
   proc sort data=origuni;
        by subject;
   run;
   data origuni;
        merge origuni
              base;
        by subject;
   run;
   %end;
   proc sort data=origuni;
        by &sort &t;
   run;
   proc transpose data=origuni out=origmult(keep=&sort &multt &b);
       by &sort;   ** DATA SET ABOVE IN MULTIVARIATE FORM **;
       id &t;
       var &v;
   run;
   proc sort data=origmult;
        by &sort;
   run;
   proc transpose data=origmult(keep=&sort &multt &b) out=datas;
       by &sort;
       var &b &multt;
   run;
   data origuni(keep=&sort &t &v);
        set datas;
        time=(substr(_NAME_,2,2))*1;
        &v=COL1;
   run;
**********************************;
 ** DATA SET IN MULTIVARIATE FORM **;
**********************************;
data &perm..omult_1;
     set origmult;
run;
proc print;run;
**********************************;
```

```
 ** DATA SET IN UNIVARIATE FORM **;
 ** WITH ALL POSSIBLE RECORDS **;
************************************;
data &perm..ouni_1;
     set origuni;
     log=ln(&v);
run;
proc print;run;

%mend data;
%data(1,abpmdif,abp,centre time patient measure drug value base,measure centre drug base
patient,time,value,_0,_1-_24,
      Vital Signs,centre time patient measure drug value base);
%data(2,diet,diet,time subject group response,group subject base,time,response,_0,_1-_9,Diet
Data,subject base);
```

```
/*************************************************************************************************

 PROGRAM: MISSDATA.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-FEB-96
Description: Lists the time points when missing data records occur
*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1 ps=55 ls=65 nodate;
*************************************************************************;
*************INPUTTING THE ORIGINAL DATA : MULTIVARIATE FORM ************;
*************************************************************************;

%MACRO MEASURE(SET,VALUE,TITLE);
options pageno=1;
   data miss;
        set abp.omult_1;
        where measure="&value";
   run;
   data ERROR1;
        set miss;
        if _1=. or _2=. or _3=. or _4=. or _5=. or _6=. or _7=. or _8=. or _9=. or _10=.
        or _11=. or _12=. or _13=. or _14=. or _15=. or _16=. or _17=. or _18=. or _19=.
        or _20=. or _21=. or _22=. or _23=. or _24=. then output error1;
   run;
   proc sort;
        by drug centre;
   run;
%macro sprint(vars,d,title2);
   proc print data=&d;
        id drug centre;
        by drug centre;
        var patient base &vars;
        title1 "Listing 2a";
        title2 "Missing Data : &title";
   run;
%mend sprint;
%sprint(_1-_6,ERROR1,);
%sprint(_7-_12,ERROR1);
%sprint(_13-_18,ERROR1);
%sprint(_19-_24,ERROR1);
   data ERROR2;
        set miss;
        if base=. then output;
   run;
   proc sort;
        by drug centre;
   run;
%sprint(_1-_6,ERROR2);
%sprint(_7-_12,ERROR2);
%sprint(_13-_18,ERROR2);
%sprint(_19-_24,ERROR2);
%MEND MEASURE;

%MEASURE(1,HR,HEART RATE);
%MEASURE(2,SBP,SYSTOLIC BP);
%MEASURE(3,DBP,DIASTOLIC BP);
   data miss;
        set diet.omult_1;
   run;
   data ERROR1;
        set miss;
        if _1=. or _2=. or _3=. or _4=. or _5=. or _6=. or _7=. or _8=. or _9=. then output error1;
   run;
   proc sort;
        by group;
   run;
%macro sprint(vars,d);
   proc print data=&d;
        var group subject base &vars;
        title1 "Listing 2a";
        title2 "Missing Data : Diet Data";
   run;
%mend sprint;
%sprint(_1-_4,ERROR1);
%sprint(_5-_9,ERROR1);
   data ERROR2;
        set miss;
        if base=. then output;
   run;
   proc sort;
        by group;
   run;
%sprint(_1-_4,ERROR2);
%sprint(_5-_9,ERROR2);
```

```
/*********************************************************************************************
Programmer: Sharayu Shanbhag
Name: MISSGENA.SAS
Date: 01 June 1996
Description: Generated missing data if possible.
Uses Permanent data set OMULT to create NOMISSM and NOMULTU
For Ambulatory Data Set.
The method used to generate a data set with no missing data was as follows:
  (a)  If a patient had greater than or equal to 20%,
  (b)  If the last observation was missing (Early Termination),
  (c)  If there was more than one missing record at the start.
  All the synario above were deleted from the data set.
  The program MISSDATA.SAS generates a listing of patients with missing data.
  This data was generated as follows:
  (1) For 1st visit missing: 2nd visit bought back.
  (2) If any one value was missing then the mean of the 2 surrounding
      values was used.
  (3) If two values were missing then the adjacent value on the left was carried
      forward and the adjacent value on the right was carried backwards.
  (4) If an even number of missing data >2 then divide number of missing values
      by 2 and carry that number back from the right and the same number forward
      from the left.
  (5) If an odd number of missing data >1 then remove 1 from the number of
      missing data and divide the remaining number by two.  Then carry that
      number back from the right and the same number forward from the left
      There should be one missing value and it can be generated as in (1).

      This was an adhoc method which was decided by Sharayu Shanbhag.
      Better methods can be found in the literature but since there were small
      numbers of missing data this method was used to save time.

*********************************************************************************************/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options ps=55 ls=65 nodate pageno=1;
   data nomissm(keep=drug centre base measure patient _0-_24 per);
        set abp.omult_1;
        if _1 gt . then v1=1;
        if _2 gt . then v2=1;
        if _3 gt . then v3=1;
        if _4 gt . then v4=1;
        if _5 gt . then v5=1;
        if _6 gt . then v6=1;
        if _7 gt . then v7=1;
        if _8 gt . then v8=1;
        if _9 gt . then v9=1;
        if _10 gt . then v10=1;
        if _11 gt . then v11=1;
        if _12 gt . then v12=1;
        if _13 gt . then v13=1;
        if _14 gt . then v14=1;
        if _15 gt . then v15=1;
        if _16 gt . then v16=1;
        if _17 gt . then v17=1;
        if _18 gt . then v18=1;
        if _19 gt . then v19=1;
        if _20 gt . then v20=1;
        if _21 gt . then v21=1;
        if _22 gt . then v22=1;
        if _23 gt . then v23=1;
        if _24 gt . then v24=1;
        sum=sum(v1,v2,v3,v4,v5,v6,v7,v8,v9,v10,v11,v12,v13,v14,v15,
                v16,v17,v18,v19,v20,v21,v22,v23,v24);
        per=100-((sum/24)*100);
        if per>=20 then delete;     ** ONLY KEEP RECORDS WITH LESS THAN 20% MISSING DATA*;
        if _24=. then delete;          ** EARLY TERMINATION (Shouldn't Analyse)***;
        if _1=. then do;
          if _2 ne . then _1=_2;
          else if _2=. then delete;     ** RECORDS DON'T BEGIN UNTIL AFTER VISIT 2 **;
        end;                            ** Shouldn't Analyse **;

        if _3=. and _2 ne . and _4 ne . then _3=mean(_2,_4);
        if _13=. and _12 ne . and _14 ne . then _13=mean(_12,_14);
        if _14=. and _13 ne . and _15 ne . then _14=mean(_13,_15);
        if _23=. and _22 ne . and _24 ne . then _23=mean(_22,_24);
        if _17 ne . and _18=. then do;
           if _19=. then do;
              if _20 ne . then do;
                 _18=_17;
                 _19=_20;
              end;
              if _20=. and _21 ne . then do;
                 _18=_17;
                 _20=_21;
                 _19=mean(_18,_20);
              end;
              if _20=. and _21=. and _22=. and _23 ne . then do;
```

```
                _18=_17;
                _19=_17;
                _22=_23;
                _21=_23;
                _20=mean(_19,_21);
              end;
           end;
        end;
        if _21 ne . and _22=. and _23=. and _24 ne . then do;
            _22=_21;
            _23=_24;
        end;
   run;
   data ERROR1;
        set nomissm;
        if per > 0 then output;
   run;
   proc sort data=ERROR1;
        by measure drug centre;
   run;
*** Lists Regenerated Data **;
%macro measure(m,title);
%macro sprint(vars,d);
   proc print data=&d;
        id drug centre;
        by drug centre;
        var patient base &vars;
        title1 "Listing 2b";
        title2 "Regenerated Data: &title";
        where measure="&m";
   run;
%mend sprint;
%sprint(_1-_6,ERROR1);
%sprint(_7-_12,ERROR1);
%sprint(_13-_18,ERROR1);
%sprint(_19-_24,ERROR1);
%mend measure;
%measure(HR,Heart Rate);
%measure(SBP,Systolic Blood Pressure);
%measure(DBP,Diastolic Blood Pressure);
   proc sort data=nomissm(drop=per);
        by measure drug centre patient base;
   run;
   proc transpose data=nomissm(keep=drug measure centre base patient _0-_24) out=datas;
        by measure drug centre patient base;
        var _0-_24;
   run;
   data nomissu(keep=drug measure centre base patient time value);
        set datas;                                          *** IN UNIVARIATE FORM ***;
        time=(substr(_NAME_,2,2))*1;
        value=COL1;
   run;
** COMPLETED DATA SETS **;
   data abp.ouni_2;
        set nomissu;
   run;
   data abp.omult_2;
        set nomissm;
   run;
   data nomissm(keep=group base subject _0-_9 per);
        set diet.omult_1;
        if _1 gt . then v1=1;
        if _2 gt . then v2=1;
        if _3 gt . then v3=1;
        if _4 gt . then v4=1;
        if _5 gt . then v5=1;
        if _6 gt . then v6=1;
        if _7 gt . then v7=1;
        if _8 gt . then v8=1;
        if _9 gt . then v9=1;
        sum=sum(v1,v2,v3,v4,v5,v6,v7,v8,v9);
        per=100-((sum/9)*100);
        if per>=20 then delete;     ** ONLY KEEP RECORDS WITH LESS THAN 20% MISSING DATA*;
        if _9=. then delete;          ** EARLY TERMINATION (Shouldn't Analyse)***;
        if _1=. then do;
          if _2 ne . then _1=_2;
          else if _2=. then delete;     ** RECORDS DON'T BEGIN UNTIL AFTER VISIT 2 **;
        end;                            ** Shouldn't Analyse **;

        if _6=. and _5 ne . and _7 ne . then _6=mean(_5,_7);
        if _8=. and _7 ne . and _9 ne . then _8=mean(_7,_9);
   run;
   data ERROR1;
        set nomissm;
        if per > 0 then output;
   run;
   proc sort data=ERROR1;
```

```
        by group;
   run;
%macro sprint(vars,d);
   proc print data=&d;
        by group;
        id group;
        var subject base &vars;
        title1 "Listing 2b";
        title2 "Regenerated Data: Diet Data";
   run;
%mend sprint;
%sprint(_1-_4,ERROR1);
%sprint(_5-_9,ERROR1);
   proc sort data=nomissm(drop=per);
        by group subject base;
   run;
   proc transpose data=nomissm(keep=group subject base _0-_9) out=datas;
       by group subject base;
       var _0-_9;
   run;
   data nomissu(keep=group base subject time response);
        set datas;                                          *** IN UNIVARIATE FORM ***;
        time=(substr(_NAME_,2,2))*1;
        response=COL1;
   run;
** COMPLETED DATA SETS **;
   data diet.ouni_2;
        set nomissu;
   run;
   data diet.omult_2;
        set nomissm;
   run;
```

```
/*************************************************************************************

Program: REDUCSUM.SAS
Programmer: Sharayu Shanbhag
Date: Dec 1995
Description: Provides the reduced data sets of summary statistics.
INPUT DATA SETS:  OUNI and NOMISSU.
Produces a data set of summary statistics by drug individual (required for PCA).
SUMP1=summaries for original data.
SUMP2=summaries for non missing data.
Produces a data set of summary statistics by drug time (required for PLOTS).
SUMT1=summaries for original data.
SUMT2=summaries for non missing data.
*************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1;
%macro both(id,id2,perm,sort,v,sort2,sub,vars);
*************************************************************************************;
 ** IN THE MACRO BELOW THE DATA SETS ARE SUMPAT1 SUMPAT2 SUMTIME1 SUMTIME2 **
 ** FOR ORIGINAL DATA (1) AND DATA AFTER MISSINGS GENERATED (2) **;
*************************************************************************************;
%macro sum1(data,a,l,g);
   ************************************************************************************;
   *********** TESTING FOR NORMALITY AT EACH TIME POINT BY TREATMENT *********************;
   **** TEST STATISTIC FOR NORMALITY. IF THE SAMPLE SIZE IS LESS THAN OR EQUAL TO 2000 IS *;
   **** SHAPIRO-WILK STATISTICOTHERWISE IS KOLMOGROV STATISTIC                          *;
   **** creates SUMM for summaries per patient ***************************************;
   ************************************************************************************;
   proc sort data=&perm..&data out=data;
        by &sort;
        where &g ne 0;       *** On Treatment Readings Only **;
   run;
   proc univariate data=data normal noprint;
        by &sort;
        var &v;
        output n=n nmiss=miss normal=norm probn=probn min=min max=max
               mean=mean std=std median=median sum=sum
               q1=q1 q3=q3
               out=SUMM
                  (keep=&sort median mean miss std q1 q3 min max miss probn n);
   run;
************************************************************************************;
*********** Data SUMPAT used to carry out PCA and Discriminant Analysis ***************;
*** Contains summaries and drug for variables by patient                ***************;
************************************************************************************;
   data &perm..sump&l._&a;
        set summ;
        change=mean-base;         *** Change in mean from baseline **;
   run;
   proc sort data=&perm..sump&l._&a out=data(keep=&sub &vars median mean base change min max q1 q3);
        by &sub &vars;
   run;
   proc transpose data=data out=tpose(keep=&sub &vars _NAME_ COL1);
        by &sub &vars;
   run;
   data data(drop=COL1 _NAME_);
        set tpose;
        value=COL1;
        variable=_NAME_;
   run;
   proc sort data=data;
        by &vars variable;
   run;
   proc univariate data=data normal noprint;
        by &vars variable;
        var value;
        output n=n probn=probn min=min max=max
               mean=mean std=std median=median sum=sum
               q1=q1 q3=q3
               out=smmean;
   run;
   data &perm..msum&l._&a;  *** Sum Stats of Sum Stats **;
        set smmean;
   run;
/*************************************************************************************
For missing data: All data summaries above will be missing if there is no data for a
patient.
In all other cases all patients have calculations for the summaries that miss out the
missing time data. The variable nmiss tells us how many missing observations there are
per patient.
*************************************************************************************/
proc sort data=&perm..&data out=data;
     by &sort2;
run;
proc univariate data=data normal noprint;
```

```
     by &sort2;
     var &v;
     output n=n nmiss=miss normal=norm probn=probn
            mean=mean std=std median=median sum=sum
            q1=q1 q3=q3 min=min max=max
            out=STATS
            (keep=&sort2 median mean miss std q1 q3 min max miss probn n);
run;
*******************************************************************************;
********** Data SUMTIME used to produce PLOTS. ********************* *****************;
*** Contains summaries and drug for variables by time    ******************;
*******************************************************************************;
data &perm..sumt&l._&a;
     set stats;
run;
%mend sum1;
%if &id=1 %then %do;
   %sum1(ouni_1,1,o,time);
   %sum1(ouni_2,2,o,time);
%end;
%if &id=2 %then %do;
  %if &id2=1 %then %do;
    %sum1(ugrp2_1,1,g2,time);
    %sum1(ugrp2_2,2,g2,time);
  %end;
  %sum1(ugrp3_1,1,g3,time);
  %sum1(ugrp3_2,2,g3,time);
%end;
%mend both;
%both(1, ,abp,measure drug centre base patient,value,measure drug time,patient centre, measure
drug);
%both(1, ,diet,group base subject,response,group time,subject,group);
%both(2,1,abp,measure drug centre base patient,value,measure drug time,patient centre, measure
drug);
%both(2,2,diet,group base subject,value,group time,subject,group);
```

```
/*************************************************************************************************

Program: SUMCENT.SAS
Programmer: Sharayu Shanbhag
Date:
Description: Same as REDUCSUM.SAS but by centre for data set A only.
*************************************************************************************************/

libname perm '/home/sshanbha/Project/abp/SSDfiles';
libname abp '/home/sshanbha/Project/abp/SSDcentre';
options pageno=1;
%macro both(id,id2,perm,sort,v,sort2,sub,vars);
*************************************************************************************;
 ** IN THE MACRO BELOW THE DATA SETS ARE SUMPAT1 SUMPAT2 SUMTIME1 SUMTIME2 **
 ** FOR ORIGINAL DATA (1) AND DATA AFTER MISSINGS GENERATED (2) **;
*************************************************************************************;
%macro sum1(data,a,l,g);
   ************************************************************************************;
   *********** TESTING FOR NORMALITY AT EACH TIME POINT BY TREATMENT *********************;
   **** TEST STATISTIC FOR NORMALITY. IF THE SAMPLE SIZE IS LESS THAN OR EQUAL TO 2000 IS *;
   **** SHAPIRO-WILK STATISTICOTHERWISE IS KOLMOGROV STATISTIC                           *;
   **** creates SUMM for summaries per patient ***************************************;
   ************************************************************************************;
   proc sort data=perm.&data out=data;
        by &sort;
        where &g ne 0;       *** On Treatment Readings Only **;
   run;
   proc univariate data=data normal noprint;
        by &sort;
        var &v;
        output n=n nmiss=miss normal=norm probn=probn min=min max=max
               mean=mean std=std median=median sum=sum
               q1=q1 q3=q3
               out=SUMM
                  (keep=&sort median mean miss std q1 q3 min max miss probn n);
   run;
*************************************************************************************;
*********** Data SUMPAT used to carry out PCA and Discriminant Analysis ***************;
*** Contains summaries and drug for variables by patient                 ***************;
*************************************************************************************;
   data &perm..sump&l._&a;
        set summ;
        change=mean-base;         *** Change in mean from baseline **;
   run;
   proc sort data=&perm..sump&l._&a out=data(keep=&sub &vars median mean base change min max q1 q3);
        by &sub &vars;
   run;
   proc transpose data=data out=tpose(keep=&sub &vars _NAME_ COL1);
        by &sub &vars;
   run;
   data data(drop=COL1 _NAME_);
        set tpose;
        value=COL1;
        variable=_NAME_;
   run;
   proc sort data=data;
        by &vars variable;
   run;
   proc univariate data=data normal noprint;
        by &vars variable;
        var value;
        output n=n probn=probn min=min max=max
               mean=mean std=std median=median sum=sum
               q1=q1 q3=q3
               out=smmean;
   run;
   data &perm..msum&l._&a;  *** Sum Stats of Sum Stats **;
        set smmean;
   run;
/*************************************************************************************
For missing data: All data summaries above will be missing if there is no data for a
patient.
In all other cases all patients have calculations for the summaries that miss out the
missing time data. The variable nmiss tells us how many missing observations there are
per patient.
*************************************************************************************;
proc sort data=perm.&data out=data;
     by &sort2;
run;


proc univariate data=data normal noprint;
     by &sort2;
     var &v;
     output n=n nmiss=miss normal=norm probn=probn
            mean=mean std=std median=median sum=sum
            q1=q1 q3=q3 min=min max=max
```

```
            out=STATS
            (keep=&sort2 median mean miss std q1 q3 min max miss probn n);
run;
*******************************************************************************;
********** Data SUMTIME used to produce PLOTS. ********************** ***************;
*** Contains summaries and drug for variables by time     ******************;
*******************************************************************************;
data &perm..sumt&l._&a;
     set stats;
run;
%mend sum1;
%if &id=1 %then %do;
   %sum1(ouni_1,1,o,time);
   %sum1(ouni_2,2,o,time);
%end;
%if &id=2 %then %do;
  %if &id2=1 %then %do;
    %sum1(ugrp2_1,1,g2,time);
    %sum1(ugrp2_2,2,g2,time);
  %end;
  %sum1(ugrp3_1,1,g3,time);
  %sum1(ugrp3_2,2,g3,time);
%end;
%mend both;
%both(1, ,abp,measure drug centre base patient,value,measure drug centre time,patient, measure
centre drug);
%both(2,1,abp,measure drug centre base patient,value,measure drug centre time,patient, measure
centre drug);
```

```
/*****************************************************************************************

Program: REDUCGRP.SAS
Programmer: Sharayu Shanbhag
Date: Jan 1996
Description:
This program looks into reducing the data set of non-missing data to get a data set containing
less than 20 observations (minimum number of patients in a group).
An ad-hoc data reduction method which was proposed by me was to get means of groups of data
over the study to use as summaries to then analyse.
Since there are 24 times of data, it is suggested that data could be grouped into 2's or 3's
and these groups could be averaged.  The average would then be used as the data to be
analysed.
Grouping into 2's would yield 12 group (Av2) observations instead of 24 time points.(MGRP2,UGRP2)
Grouping into 3's would yield 8 group (Av3) observations instead of 24 time points. (MGRP3,UGRP3)
Summary Statistics were found by measure drug group (Av2) = SUMGRP2
Summary Statistics were found by measure drug group (Av3) = SUMGRP3
Note: This method could also be applied to data sets with single missing data points
      since the average would be calculated of the remaining data (excluding the missing data).

*****************************************************************************************/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1;
*****************************************************************************************;
****** THE FOLLOWING MACRO CREATES MGRP,UGRP & SUMGRP FOR NON MISSING DATA         ****;
*****************************************************************************************;

%macro group(data,v,v2);
   data abp.MGRP2_&v(keep=measure drug centre patient base GRP1-GRP12);
        set abp.&data;                ** IN MULTIVARIATE FORM ***;
                                     **  MAKES THREE OBSERVATIONS INTO ONE OBS BY AVERAGING**;
        GRP1=mean(_1,_2);
        GRP2=mean(_3,_4);
        GRP3=mean(_5,_6);
        GRP4=mean(_7,_8);
        GRP5=mean(_9,_10);
        GRP6=mean(_11,_12);
        GRP7=mean(_13,_14);
        GRP8=mean(_15,_16);
        GRP9=mean(_17,_18);
        GRP10=mean(_19,_20);
        GRP11=mean(_21,_22);
        GRP12=mean(_23,_24);
        output;
   run;

proc sort data=abp.mgrp2_&v out=mgrp;
     by measure drug centre patient base;
run;

proc transpose data=mgrp(keep=measure drug centre patient base GRP1-GRP12)
out=grp(rename=(COL1=value));
    by measure drug centre patient base;
    var GRP1-GRP12;
run;

data abp.UGRP2_&v(keep=measure patient centre drug base time t value av2); *** SAME AS GRPMEAN ***;
     set grp;                                                                *** IN UNIVARIATE FORM
**;
     t=1*(substr(_NAME_,4,2));
     time=t;
     av2=value;
run;
*****************************************************************************************;
*********** Data SUMGRPT (2) used to produce PLOTS*********************;
*********** Data SUMGRPP (2) used to produce SUMMARY LISTING ALSO TESTED *;
*** Contains summaries and drug for variables by grouped (Av2)times  **********;
*****************************************************************************************;

   data abp.MGRP3_&v(keep=measure drug centre patient base GRP1-GRP8);
        set abp.&data;                ** IN MULTIVARIATE FORM ***;
                                     **  MAKES THREE OBSERVATIONS INTO ONE OBS BY AVERAGING**;
        GRP1=mean(_1,_2,_3);
        GRP2=mean(_4,_5,_6);
        GRP3=mean(_7,_8,_9);
        GRP4=mean(_10,_11,_12);
        GRP5=mean(_13,_14,_15);
        GRP6=mean(_16,_17,_18);
        GRP7=mean(_19,_20,_21);
        GRP8=mean(_22,_23,_24);
        output;
   run;
   data diet.MGRP3_&v(keep=group subject base GRP1-GRP3);
        set diet.&data;               ** IN MULTIVARIATE FORM ***;
                                     **  MAKES THREE OBSERVATIONS INTO ONE OBS BY AVERAGING**;
        GRP1=mean(_1,_2,_3);
```

```
        GRP2=mean(_4,_5,_6);
        GRP3=mean(_7,_8,_9);
        output;
   run;
%macro grp3(perm,uval,vals,sort);
proc sort data=&perm..mgrp3_&v out=mgrp;
     by &vals base;
run;

proc transpose data=mgrp(keep=&vals base GRP1-&uval) out=grp(rename=(COL1=value));
    by &vals base;
    var GRP1-&uval;
run;

data &perm..UGRP3_&v(keep=&vals base t value time av3);     *** SAME AS GRPMEAN ***;
     set grp;                                                      *** IN UNIVARIATE FORM **;
     t=1*(substr(_NAME_,4,1));
     time=t;
     av3=value;
run;

%mend grp3;
%grp3(abp,GRP8,measure drug centre patient,measure drug);
%grp3(diet,GRP3,group subject,group);
%mend group;

%group(omult_1,1);
%group(omult_2,2);
```

```
/*************************************************************************************************

 PROGRAM: REDUCPCA.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-96
 Description:A PCA was conducted to reduce the components in TPOSED from 24 to something lower.
   Here the option COV was used since all data was in the same units.
            option NOINT stopped the data from removing the mean.
*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1 ps=63 ls=78 nodate;
*************************************************************************;
*************INPUTTING THE ORIGINAL DATA : DATA ************************;
/*************************************************************
******** CONDUCTING PCA ON DATA SETS ****************************
%macro anal(pca,pca2,data,v,title,n,n2);
proc sort data=abp.&data out=new;
     by measure &pca;
run;
proc princomp data=new cov noint noprint out=pca outstat=corr;
  by measure &pca;
  var _1-_24;
  title1 "PCA FOR ALL DATA: &title";
run;
data abp.corr_&v;
   set corr;
   rename _TYPE_=type;
   rename _NAME_=test;
run;
data abp.pca_&v(keep=measure patient drug prin1-prin24);    *** KEEP ONLY REQUIRES PRIN COMPS **;
     set pca;
run;
%macro vital(app,vital,m);
data corr;
     set abp.corr_&v;
     where measure="&m";
run;
proc sort data=corr;
     by &pca;
run;
%MACRO SPRINT2(a,vars,type,tit);
proc print data=corr;
  where type="&type";
  id &pca;
  by &pca;
  var test &vars;
  title1 "APPENDIX &app";
  title2 "Listing &a.&n";
  title3 "P.C.A.: &tit : &type for &vital";
  title4 "&title";
run;
title;
%MEND SPRINT2;
/*
%sprint2(7,_1-_6,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_7-_12,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_13-_18,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_19-_24,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_1-_6,EIGENVAL,Eigen-Vectors and Eigen-Values);
%sprint2(7,_7-_12,EIGENVAL,Eigen-Vectors and Eigen-Values);
%sprint2(7,_13-_18,EIGENVAL,Eigen-Vectors and Eigen-Values);
%sprint2(7,_19-_24,EIGENVAL,Eigen-Vectors and Eigen-Values);

%sprint2(8,_1-_6,N,N);
%sprint2(8,_7-_12,N,N);
%sprint2(8,_13-_18,N,N);
%sprint2(8,_19-_24,N,N);
%sprint2(8,_1-_6,MEAN,Mean);
%sprint2(8,_7-_12,MEAN,Mean);
%sprint2(8,_13-_18,MEAN,Mean);
%sprint2(8,_19-_24,MEAN,Mean);
*/
*%sprint2(8,_1-_6,STD);    **** ONLY COMPUTE FOR THE OPTION TYPE=CORR **;
*%sprint2(8,_7-_12,STD);   **** NA **;
*%sprint2(8,_13-_18,STD);
*%sprint2(8,_19-_24,STD);
/*
%sprint2(8,_1-_6,UCOV,Unstructured Covariance Matrix);
%sprint2(8,_7-_12,UCOV,Unstructured Covariance Matrix);
%sprint2(8,_13-_18,UCOV,Unstructured Covariance Matrix);
%sprint2(8,_19-_24,UCOV,Unstructured Covariance Matrix);
*/
%MACRO SPRINT(vars);

data pca;
```

```
     set abp.pca_&v;
     where measure="&m";
run;

proc sort data=corr;
     by &pca;
run;
proc print data=pca;
  var patient &vars;
  by &pca;
  id &pca;
  title1 "APPENDIX &app";
  title2 "Listing &n2";
  title3 "P.C.A.: Principal Components For &vital";
  title4 "&title";
run;
title;
%MEND SPRINT;
/*
%sprint(_1-_6);
%sprint(_7-_12);
%sprint(_13-_18);
%sprint(_19-_24);
*/
%sprint(PRIN1-PRIN5);
%sprint(PRIN6-PRIN10);
/*
%sprint(PRIN7-PRIN12);
%sprint(PRIN13-PRIN18);
%sprint(PRIN19-PRIN24);
*/
%mend vital;
%vital(A,Heart Rate,HR);
%vital(B,Systolic Blood Pressure,SBP);
%vital(C,Diastolic Blood Pressure,DBP);

proc sort data=diet.&data out=new;
     by &pca2;
run;

proc princomp data=new cov noint noprint out=pca outstat=corr;
  by &pca2;
  var _1-_9;
  title1 "PCA FOR ALL DATA: &title";
run;
data diet.corr_&v;
   set corr;
   rename _TYPE_=type;
   rename _NAME_=test;
run;
data diet.pca_&v(keep=subject group prin1-prin9);    *** KEEP ONLY REQUIRES PRIN COMPS **;
     set pca;
run;
data corr;
     set diet.corr_&v;
run;

proc sort data=corr;
     by &pca2;
run;
%MACRO SPRINT2(a,vars,type,tit);
proc print data=corr;
  where type="&type";
  id &pca2;
  by &pca2;
  var test &vars;
  title1 "APPENDIX D";
  title2 "Listing &a.&n";
  title3 "P.C.A.: &tit : &type for Dietary Data";
  title4 "&title";
run;
title;
%MEND SPRINT2;
/*
%sprint2(7,_1-_4,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_5-_9,USCORE,Eigen-Vectors and Eigen-Values);
%sprint2(7,_1-_4,EIGENVAL,Eigen-Vectors and Eigen-Values);
%sprint2(7,_5-_9,EIGENVAL,Eigen-Vectors and Eigen-Values);

%sprint2(8,_1-_4,N,N);
%sprint2(8,_5-_9,N,N);
%sprint2(8,_1-_4,MEAN,Mean);
%sprint2(8,_5-_9,MEAN,Mean);

*%sprint2(8,_1-_4,STD);    **** ONLY COMPUTE FOR THE OPTION TYPE=CORR **;
*%sprint2(8,_4-_9,STD);   **** NA **;
%sprint2(8,_1-_4,UCOV,Unstructured Covariance Matrix);
```

```
%sprint2(8,_5-_9,UCOV,Unstructured Covariance Matrix);
*/
%MACRO SPRINT(vars);


proc sort data=diet.pca_&v out=pca;
   by &pca2;
run;
proc print data=pca;
  var subject &vars;
  by &pca2;
  id &pca2;
  title1 "APPENDIX D";
  title2 "Listing &n2";
  title3 "P.C.A.: Principal Components For Dietary Data";
  title4 "&title";
run;
title;
%MEND SPRINT;
/*
%sprint(_1-_4);
%sprint(_5-_9);
*/
%sprint(PRIN1-PRIN5);
*%sprint(PRIN6-PRIN9);

%mend anal;

*%anal(drug,group,omult_1,1,Original Data,a,5);
%anal(drug,group,omult_2,2,After Data Replaced,b,5);
```

```
/*************************************************************************************************
 PROGRAM: ANALDATA.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-97
 Creates permanent data set MANAL_1 and MANAL_2 for each data set 1 and 2.
These are the final multivariate data sets used for analysis purposes.
*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
%include '/home/sshanbha/Project/macros/formats.sas';
%include '/home/sshanbha/Project/macros/anal.sas';
options pageno=1 ps=55 ls=80;
%macro type(i,title2);
%macro data(id,perm,vars,times,time2,time3);
data orig(keep=&vars &times);
     set &perm..omult_&i;
run;
proc sort data=orig;
     by &vars;
run;
data sum;
     set &perm..sumpo_&i(keep=&vars base mean median min max q1 q3 change);
run;
proc sort data=sum;
     by &vars;
run;
data osum;
     merge orig(in=a)
           sum;
     by &vars;
     if a;
run;
data grp3(keep=&vars &time2);
     set &perm..mgrp3_&i;                    ** WANT SEPERATE VARIABLE NAMES**;
     rename GRP1=g1
            GRP2=g2
            GRP3=g3;
     if &id=1 then do;
     rename GRP4=g4
            GRP5=g5
            GRP6=g6
            GRP7=g7
            GRP8=g8;
     end;
run;
proc sort data=grp3;
     by &vars;
run;
data sum3(keep=&vars mean3 med3 min3 max3 q1_3 q3_3 change3);
     set &perm..sumpg3_&i(keep=&vars mean median min max q1 q3 change);
     rename mean=mean3
            median=med3
            min=min3
            max=max3
            q1=q1_3
            q3=q3_3
            change=change3;
run;
proc sort data=sum3;
     by &vars;
run;
data g3sum;
     merge grp3(in=a)
           sum3;
     by &vars;
     if a;
run;
data allsum;
     merge osum(in=a)
           g3sum;
     by &vars;
     if a;
run;
%if &id=1 %then %do;

data grp2(keep=&vars &time3);
     set &perm..mgrp2_&i;
run;
proc sort data=grp2;
     by &vars;
run;
data sum2(keep=&vars mean2 med2 min2 max2 q1_2 q3_2 change2);
     set &perm..sumpg2_&i(keep=&vars mean median min max q1 q3 change);
     rename mean=mean2
            median=med2
            min=min2
```

```
            max=max2
            q1=q1_2
            q3=q3_2
            change=change2;
run;
proc sort data=sum2;
     by &vars;
run;
data g2sum;
     merge grp2(in=a)
           sum2;
     by &vars;
     if a;
run;
data allsum;
     merge allsum(in=a)
           g2sum;
     by &vars;
     if a;
run;
%end;
data &perm..manal_&i;
     set allsum;
run;
%mend data;
%data(1,abp,measure drug centre patient,_0-_24,G1-G8,GRP1-GRP12);
%data(2,diet,group subject,_0-_9,G1-G3,);
%mend type;
%type(1,Original);
%type(2,After Replaced);
```

```
/*************************************************************************************************
 PROGRAM: CATDATA.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-97
 ONLY CONDUCTED ON VITAL SIGNS DATA
 CATEGORISES THE NUMBER OF OCCURRENCES OF NORMAL, ABNORMAL (HIGH AND LOW) READINGS
 The input data sets is: DB.OUNI and NOMISSU
 The output data sets were : DB.CAT1 and CAT2 and DB.ABN1 and ABN2.
 Creates multivariate data sets for categorical data analysis
*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
%include '/home/sshanbha/Project/macros/formats.sas';
%include '/home/sshanbha/Project/macros/anal.sas';
options pageno=1 ps=55 ls=80;
*************************************************************************;
***************** INPUTTING THE DATA ************************************;
*************************************************************************;
title ' ';

%macro data(data,outcat,outabn,outbase,v);

data base(keep=measure patient centre drug time value);
     set abp.&data;
     time=0;
     value=base;
run;
proc sort data=base nodupkey;
   by measure patient centre drug;
run;
data cat(keep=measure patient centre drug abnormal time category);       ** a data set with time=0-
24**;
     set abp.&data
         base;
     if value > 0 then do;          ** CATEGORY:missing, 1-7 for each variable category **;
       if measure='HR' then do;     ** ABNORMAL:missing -1, 0 or 1 **;
         if value < 60 then do;
            abnormal=-1;
            if value >= 40 then category=1;
         end;
         else if value < 100 then do;
           abnormal=0;
           if value < 80 then category=2;
           else category=3;
         end;
         else if value >= 100 then do;
            abnormal=1;
            if value < 120 then category=4;
            else if value < 140 then category=5;
            else if value < 160 then category=6;
            else category=7;
         end;
         output;
       end;
       else if measure='SBP' then do;
         if value < 100 then do;
            abnormal=-1;
            if value >= 80 then category=1;
         end;
         else if value < 140 then do;
           abnormal=0;
           if value < 130 then category=2;
           else category=3;
         end;
         else if value >= 140 then do;
            abnormal=1;
            if value < 160 then category=4;
            else if value < 180 then category=5;
            else if value < 210 then category=6;
            else category=7;
         end;
         output;
       end;
       else if measure='DBP' then do;
         if value < 60 then do;
            abnormal=-1;
            if value >= 40 then category=1;
         end;
         else if value < 90 then do;
           abnormal=0;
           if value < 85 then category=2;
           else category=3;
         end;
         else if value >= 90 then do;
            abnormal=1;
            if value lt 100 then category=4;
            else if value lt 110 then category=5;
```

```
            else if value lt 120 then category=6;
            else category=7;
          end;
          output;
        end;
      end;
      else do;
        category=.;
        abnormal=.;
      end;
run;
data outcat
      outbase;                                          ** low,normal and high ,**;
          set cat;                                          ** values missing,0 or 1 **;
          if abnormal=. then low=.;
          else if abnormal=-1 then low=1;
          else low=0;
          if abnormal=. then high=.;
          else if abnormal=1 then high=1;
          else high=0;
          if abnormal=. then normal=.;
          else if abnormal=0 then normal=1;
          else normal=0;
          format category BP. abnormal abn. low high normal yesn.;
          if time=0 then output outbase;
          output outcat;
run;
proc sort data=outcat out=sort;
    by measure drug centre patient;
    where time ne 0;
run;
proc univariate data=sort(drop=time) noprint;
      by measure drug centre patient;
      var low normal high;
      output sum=nl nn nh out=tot;** Number of low, high and normal responses through the study**;
run;
data outabn;
    set tot;
    n=sum(nl,nn,nh);
    if measure in ('SBP','DBP') then do;
       if 0 <= nh <= 12 then freq=1;
       else if 12 < nh <= 18 then freq=2;
       else if 18 < nh <= 24 then freq=3;
       if freq in(2,3) then halfabn=1;
       else halfabn=0;
       if freq in(3) then qrtabn=1;
       else qrtabn=0;
       format freq frqa.;
       output;
    end;
    if measure in ('HR') then do;
       if nh=0 then freq2=1;
       else if 0 < nh <= 3 then freq2=2;
       else if 3 < nh <= 6 then freq2=3;
       format freq2 frqb.;
       output;
    end;
run;
proc sort data=outcat out=abp.u&outcat;
      by measure drug centre patient time;
run;

proc transpose data=abp.u&outcat out=mult;
      by measure drug centre patient;
      id time;
      var high;
run;
proc sort data=outabn out=abp.u&outabn;
      by measure drug centre patient;
run;


proc sort data=outbase out=abp.u&outbase;
      by measure drug centre patient;
run;

data abp.mhigh&v;
      merge mult(keep=measure drug centre patient _0 _1-_24)
            abp.u&outabn(keep=measure drug centre patient n halfabn qrtabn freq freq2 nh nl nn)
            abp.u&outbase(keep=measure drug centre patient high);
      by measure drug centre patient;
run;
%mend data;
%data(ouni,cat1,abn1,cbase1,_1);
%data(nomissu,cat2,abn2,cbase2,_2);
```

```
/*************************************************************************************************

 PROGRAM: DISCRIM.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-96
 A Discriminant Analysis was conducted on the data sets for
 PCA's (PCAa for drug & PCAb for centre drug)
 SUMPAT's (Summaries across patients)
 GRP's (MGRP2 and MGRP3);

*************************************************************************************************/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1 ps=66 ls=80 nodate;
%macro candisc (anal,c,var,tit);
%macro meas(m,mtit);
proc sort data=abp.&anal out=disc;
     by measure;
     where measure="&m";
run;
 proc candisc data=disc(keep=patient drug &var) outstat=cdisc1 distance;
      class drug;
      var &var;
  title1 "Discriminant Analysis: &tit";
 run;
title ' ';
%mend meas;
%meas(HR,Heart Rate (beats/min));
%meas(SBP,Systolic Blood Pressure (mmHg));
%meas(DBP,Diastolic Blood Pressure (mmHg));
%mend candisc;
%candisc(omult_1,od_1,_1-_24,Original Data Before Missing Data Replaced);
%candisc(omult_2,od_2,_1-_24,Original Data After Missing Data Replaced);
%candisc(sumpo_1,os_1,mean median max min q1 q3, Summaries of Original Data Before Missing Data
Replaced);  ** 13 obs dropped **;
%candisc(sumpo_2,os_2,mean median max min q1 q3, Summaries of Original Data After Missing Data
Replaced);
%candisc(pca_1,op_1,prin1 prin2 prin3 prin4 prin5 prin6 prin7 prin8 prin9 prin10,PCA on Original
Data Before Missing Data Replaced);
%candisc(pca_2,op_2,prin1 prin2 prin3 prin4 prin5 prin6 prin7 prin8 prin9 prin10,PCA on Original
Data After Missing Data Replaced);
%candisc(mgrp3_1,og3_1,GRP1-GRP8,Average Grouped In Threes for Data Before Missing Data Replaced);
%candisc(mgrp3_2,og3_2,GRP1-GRP8,Average Grouped In Threes for Data After Missing Data Replaced);
%candisc(sumpg3_1,g3s_1,mean median max min q1 q3, Summaries of Average of 3 Data Before Missing
Data Replaced);  ** 13 obs dropped **;
%candisc(sumpg3_2,g3s_2,mean median max min q1 q3, Summaries of Average of 3 After Missing Data
Replaced);
%candisc(mgrp2_1,og2_1,GRP1-GRP12,Average Grouped In Pairs for Data Before Missing Data Replaced);
%candisc(mgrp2_2,og2_2,GRP1-GRP12,Average Grouped In Pairs for Data After Missing Data Replaced);
%candisc(sumpg2_1,g2s_1,mean median max min q1 q3, Summaries of Average of 2 Before Missing Data
Replaced);  ** 13 obs dropped **;
%candisc(sumpg2_2,g2s_2,mean median max min q1 q3, Summaries of Average of 2 After Missing Data
Replaced);
%macro candisc (anal,c,var,tit);
proc sort data=diet.&anal out=disc;
     by group;
run;

 proc candisc data=disc(keep=subject group &var) outstat=cdisc1 distance;
      class group;
      var &var;
  title1 "Discriminant Analysis: &tit";
  title2 "Dietary Data";
 run;
title ' ';
%mend candisc;
%candisc(omult_1,od_1,_1-_9,Original Data Before Missing Data Replaced);
%candisc(omult_2,od_2,_1-_9,Original Data After Missing Data Replaced);
%candisc(sumpo_1,os_1,mean median max min q1 q3, Summaries of Original Data Before Missing Data
Replaced);  ** 13 obs dropped **;
%candisc(sumpo_2,os_2,mean median max min q1 q3, Summaries of Original Data After Missing Data
Replaced);
%candisc(pca_1,op_1,prin1 prin2 prin3 prin4 prin5,PCA on Original Data Before Missing Data
Replaced);
%candisc(pca_2,op_2,prin1 prin2 prin3 prin4 prin5,PCA on Original Data After Missing Data Replaced);
%candisc(mgrp3_1,og3_1,GRP1-GRP3,Average Grouped In Threes for Data Before Missing Data Replaced);
%candisc(mgrp3_2,og3_2,GRP1-GRP3,Average Grouped In Threes for Data After Missing Data Replaced);
%candisc(sumpg3_1,g3s_1,mean median max min q1 q3, Summaries of Average of 3 Data Before Missing
Data Replaced);  ** 13 obs dropped **;
%candisc(sumpg3_2,g3s_2,mean median max min q1 q3, Summaries of Average of 3 After Missing Data
Replaced);
```

```
/*************************************************************************************************

 PROGRAM: LOGISTIC.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-97

 Conducts Logistic Regression on the Data.
*************************************************************************************************/

libname db '/home/sshanbha/Project/abp/SSDfiles';
options pageno=1 ps=66 ls=80 nodate;
%include '~/Project/macros/formats.sas';
*************************************************************************;
***************** INPUTTING THE DATA ************************************;
*************************************************************************;
%macro measure(m,title2);
%macro var(var,title);
proc sort data=db.mhigh_1 out=base;
     by measure centre drug ;
     where measure="&m";
run;

proc freq data=base noprint;
     tables drug*&var/ out=a;
     by measure centre;
run;
data setd;
     set a;
     icentre=(centre=1);
     ia=(drug=1);
     ib=(drug=2);
     ic=(drug=3);
     inta=icentre*ia;
     intb=icentre*ib;
     intc=icentre*ic;
run;
proc logistic descending;
     freq count;
     model &var = icentre ia ib ic inta intb intc;
     title "Full Model: &title &title2";
run;
proc logistic descending;
     freq count;
     model &var = icentre ia ib ic / scale=none
           aggregate risklimits;
     title "Reduced Model: &title &title2";
run;
%mend var;
%var(halfabn,50% Abnormal Readings);
%var(qrtabn,75% Abnormal Readings);

%mend measure;
%measure(SBP,Systolic BP);
%measure(DBP,Diastolic BP);
*%measure(HR,Heart Rate);
```

```
/*****************************************************************************
 PROGRAM: ORIGMOD.SAS
Models on the original complete dataset.
*****************************************************************************/
libname abp '~/Project/abp/SSDfiles';
libname diet '~/Project/diet/SSDfiles';
options nodate nonumber ps=80 ls=65;
%macro test(t,var,title,out);
*%include '/home/sshanbha/macros/macros.sas';

data uni1;
     set abp.ouni_1;
     where measure="&title";
run;
data uni1;
     set uni1;
     if time ne 0;
run;
title1 'Model: Adjust for Time, Centre and Base';
data uni2;
     set abp.ouni_2;
     where measure="&title";
run;
data uni2;
     set uni2;
     if time ne 0;
run;
/*
title2 "&title : Original Data";
proc mixed data=uni1 noclprint;
     class patient centre time drug;
     model value=centre base time drug drug*time;
     repeated/sub=patient type=CS;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;

*/
title2 "&title : Original Data :No centre";
proc mixed data=uni1 noclprint;
     class patient time drug;
     model value=base time drug drug*time;
     repeated/sub=patient type=CS;
   contrast 'G 1 vs G2' drug 1 -1 0 0;
   contrast 'G 1 vs G3' drug 1 0 -1 0;
   contrast 'G 1 vs G4' drug 1 0 0 -1;
   contrast 'G 2 vs G3' drug 0 1 -1 0;
   contrast 'G 2 vs G4' drug 0 1 0 -1;
   contrast 'G 3 vs G4' drug 0 0 1 -1;
     lsmeans time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=abp.m1_&t;
run;
 *  random int /subject=idno type=UN;

/*
title2 "&title : After Missing Replaced";
proc mixed data=uni2 noclprint;
     class patient centre time drug;
     model value=centre base time drug drug*time;
     repeated/sub=patient type=CS;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;

title2 "&title : After Missing Replaced: No Center";
proc mixed data=uni2 noclprint;
     class patient time drug;
     model value=base time drug drug*time;
     repeated/sub=patient type=CS;
     lsmeans time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;
*/
%mend test;


%test(1,hr,HR,hrout);
%test(2,sbp,SBP,sbpout);
%test(3,dbp,DBP,dbpout);


data uni1;
     set diet.ouni_1;
run;
data uni1;
     set uni1;
     if time ne 0;
```

```
run;
title1 'Model: Adjust for Time and Base';
data uni2;
     set diet.ouni_2;
run;
data uni2;
     set uni2;
     if time ne 0;
run;
title2 "&title : Original Data";
proc mixed data=uni1 noclprint;
     class subject time group;
     model response=base time group group*time;
     repeated/sub=subject type=CS;
   contrast 'G 1 vs G2' group 1 -1 0;
   contrast 'G 1 vs G3' group 1 0 -1;
   contrast 'G 2 vs G3' group 0 1 -1;
     lsmeans time group group*time / alpha=0.05 cl;
     make 'lsmeans' out=diet.m1_4;
run;
/*
title2 "&title : After Missing Replaced";
proc mixed data=uni2 noclprint;
     class subject time group;
     model response=base time group group*time;
     repeated/sub=subject type=CS;
     lsmeans time group group*time / alpha=0.05 cl;
     make 'lsmeans' out=dietout;
run;
*/
```

```
/*************************************************************************************************
 PROGRAM: AVMODEL.SAS
Models the Average Reduced Data.
This program models data set A after adjusting for centre time and baseline reading also.
models data set B after adjusting for time and baseline reading also.
Then removes centre and then baseline.
*************************************************************************************************/
libname abp '~/Project/abp/SSDfiles';
libname diet '~/Project/diet/SSDfiles';
options nodate nonumber ps=80 ls=65;
%macro test(t,var,title,out);
*%include '/home/sshanbha/macros/macros.sas';

data uni1(drop=measure);
     set abp.ugrp2;
     rename group=time av2=value;
     where measure="&title";
run;
data uni2(drop=measure);
     set abp.ugrp3;
     rename group=time av3=value;
     where measure="&title";
run;
/*
title1 'Model: Adjust for Time and centre for Group 2';
title2 "&title";
proc mixed data=uni1 noclprint;
     class patient centre time drug;
     model value=centre time drug drug*time;
     repeated/sub=patient type=UN;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;

title1 'Model: Adjust for Time, Centre and Base for Group 2';
title2 "&title";
proc mixed data=uni1 noclprint;
     class patient centre time drug;
     model value=centre base time drug drug*time;
     repeated/sub=patient type=UN;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;
*/
title1 'Model: Adjust for Time, and Base for Group 2';
title2 "&title";
proc mixed data=uni1 noclprint;
     class patient time drug;
     model value=base time drug drug*time;
     repeated/sub=patient type=UN;
   contrast 'G 1 vs G2' drug 1 -1 0 0;
   contrast 'G 1 vs G3' drug 1 0 -1 0;
   contrast 'G 1 vs G4' drug 1 0 0 -1;
   contrast 'G 2 vs G3' drug 0 1 -1 0;
   contrast 'G 2 vs G4' drug 0 1 0 -1;
   contrast 'G 3 vs G4' drug 0 0 1 -1;
     lsmeans time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=abp.M2_&t;
run;
/*
title1 'Model: Adjust for Time and centre for Group 3';
title2 "&title";
proc mixed data=uni2 noclprint;
     class patient centre time drug;
     model value=centre time drug drug*time;
     repeated/sub=patient type=UN;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;

title1 'Model: Adjust for Time, Centre and Base for Group 3';
title2 "&title";
proc mixed data=uni2 noclprint;
     class patient centre time drug;
     model value=centre base time drug drug*time;
     repeated/sub=patient type=UN;
     lsmeans centre time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=&out;
run;
*/
title1 'Model: Adjust for Time, Base for Group 3';
title2 "&title";
proc mixed data=uni2 noclprint;
     class patient time drug;
     model value=base time drug drug*time;
     repeated/sub=patient type=UN;
   contrast 'G 1 vs G2' drug 1 -1 0 0;
```

```
   contrast 'G 1 vs G3' drug 1 0 -1 0;
   contrast 'G 1 vs G4' drug 1 0 0 -1;
   contrast 'G 2 vs G3' drug 0 1 -1 0;
   contrast 'G 2 vs G4' drug 0 1 0 -1;
   contrast 'G 3 vs G4' drug 0 0 1 -1;
     lsmeans time drug drug*time / alpha=0.05 cl;
     make 'lsmeans' out=abp.M3_&t;
run;
%mend test;


%test(1,hr,HR,hrout);
%test(2,sbp,SBP,sbpout);
%test(3,dbp,DBP,dbpout);
data uni3(drop=measure);
     set diet.ugrp3;
     rename grp=time av3=value;
run;
/*
title1 'Model: Adjust for Time for Group 3';
title2 "Diet Data";
proc mixed data=uni3 noclprint;
     class subject time group;
     model value=time group group*time;
     repeated/sub=subject type=UN;
     lsmeans time group group*time / alpha=0.05 cl;
     make 'lsmeans' out=dietout;
run;
*/
title1 'Model: Adjust for Base and Time for Group 3';
title2 "Diet Data";
proc mixed data=uni3 noclprint;
     class subject time group;
     model value=time base group group*time;
     repeated/sub=subject type=UN;
   contrast 'G 1 vs G2' group 1 -1 0;
   contrast 'G 1 vs G3' group 1 0 -1;
   contrast 'G 2 vs G3' group 0 1 -1;
     lsmeans time group group*time / alpha=0.05 cl;
     make 'lsmeans' out=diet.M3_4;
run;
```

```
/*************************************************************************************************

 PROGRAM: KMANAL.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-97

 Produces Survival Estimates Using K.Meier Cummulative Event Rates.
 Plots These Data As A Survival Curve.

*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
%include '/home/sshanbha/Project/macros/formats.sas';
%include '/home/sshanbha/macros/macros2.sas';
options pageno=1 ps=66 ls=80 nodate;
%macro measure(id,m,title,App);

data all;
     set abp.ucat1;
     if high=1 then event=1;
     else event=0;
     if measure="&m" and time ne 0 then output;
run;

proc sort data=all;
     by drug patient descending event time;
run;
data last;
     set all;
     by drug patient descending event time;
     if event=0 then tos=24;
     else tos=time;
     if first.patient then output;
run;

%km2(last,event,tos,drug,Time To Abnormality);
%km(last,event,kmtest,tos,drug,Hours);
%kmplot(kmtest,surv_p,survtime,drug,treat.,DRUG,Time on Study (Hours),0,24,1,
        % Survival,0,100,10,&title,Time To First Abnormal Reading,1,1._&id);
%mend measure;
%measure(1,SBP,Systolic BP (mmHg),B);
%measure(2,DBP,Diastolic BP (mmHg),C);
%measure(3,HR,Heart Rate (beats/min),A);
```

```
/*************************************************************************************************

 PROGRAM: CATANAL.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-AUG-97

 Produces cross tabulations of categorical data and tests using chisquared tests
*************************************************************************************************/

libname db '/home/sshanbha/Project/abp/SSDfiles';
options pageno=1 ps=66 ls=80 nodate;
*************************************************************************;
***************** INPUTTING THE DATA ************************************;
*************************************************************************;
%macro data(abn,cat,base,title);

proc sort data=db.&base out=base;
     by measure drug ;
run;
proc freq data=base;
     tables drug*abnormal/exact;
     by measure;
     TITLE1 "TESTS FOR RELATIONSHIP BETWEEN DRUG AND CATEGORIES AT BASELINE";
     title2 "&title";
run;
proc sort data=db.&cat out=cat;
     by measure time;
run;
proc freq data=cat;
     tables abnormal*drug/chisq;
     by measure time;
     TITLE1 "TESTS FOR RELATIONSHIP BETWEEN DRUG AND CATEGORIES AT EACH TIME POINT";
     title2 "&title";
run;
title ' ';

%macro hln(v,tit);
proc freq data=base;
     tables &v*drug/exact;
     by measure;
     TITLE1 "TESTS FOR RELATIONSHIP BETWEEN DRUG AND &tit VALUES AT BASELINE ";
     title2 "&title";
run;
%mend hln;
%hln(high,HIGH);


proc freq data=db.&abn;
     tables freq*drug/chisq;
     by measure;
     where measure in ('SBP','DBP');
     TITLE1 "TESTS FOR RELATIONSHIP BETWEEN DRUG AND ABNORMALITY";
     title2 "&title";
run;

proc freq data=db.&abn;
     tables freq2*drug/exact;
     by measure;
     where measure in ('HR');
     TITLE1 "TESTS FOR RELATIONSHIP BETWEEN DRUG AND ABNORMALITY";
     title2 "&title";
run;

%mend data;
%data(abn1,cat1,cbase1,ORIGINAL DATA);
*%data(abn2,cat2,cbase2,REGENERATED DATA);
```

```
/*************************************************************************************************
 PROGRAM: STIMEPLT.SAS
 PROGRAMMER: SHARAYU
 DATE: 10-JAN-
 Produces Plots of Mean, median, min and max over time for time(0 to 24) for original data
 and time 1 to 12 for average group 2 and time 1 to 8 for average group 3 for Vital sign data.
*************************************************************************************************/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
libname graph '/home/sshanbha';
options pageno=1;
%include '/home/sshanbha/Project/macros/formats.sas';
%macro when(ds,titw);
%macro graph(drg,lab,fig,app,no,title,data,l2,u2,value,summ,tit2,l,u,b,unit,foot);
%if &lab=1 %then %do;
data GRAPHST;
     set abp.&data._&ds;
     mean=round(mean,0.1);
     median=round(median,0.1);
     if measure="&value" then output;
run;
%end;
%if &lab=2 %then %do;
data GRAPHST;
     set diet.&data._&ds;
     mean=round(mean,0.1);
     median=round(median,0.1);
run;
%end;
filename gsasfile "/home/sshanbha/GIF1/ &no._&ds..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss


       autofeed
        cback=white

symbol1 color=black interpol=spline width=0.5 value=dot height=1
symbol2 color=black interpol=spline width=0.5 value=circle height=1
symbol3 color=black interpol=spline width=0.5 value=square height=1
symbol4 color=black interpol=spline width=0.5 value=triangle height=1
axis1 label=(h=0.2in "TIME &unit") order=(&l2 to &u2 by 1) offset=(2) width=3 c=black;
axis2 label=(h=0.2in angle=90 "&title") order=( &l to &u by &b ) offset=(2) width=3 c=black;
proc gplot data=graphst;
    * title1 c=black h=2.0 "Appendix &app";
    *  title2 c=black h=2.0 "Figure &fig";
     title1 c=black h=1.5 "Plot Of &tit2 Over Time By
     title2 c=black h=1.5
     plot
     / haxis=axis1 vaxis=axis2 hminor=0 vminor=0 caxis=black frame
     footnote j=l c=black h=1.5 "NOTE: &foot &titw Missing Data Replaced";
run;
footnote '
title '

quit;
run;
%mend graph;
%if &ds=1 %then %do;
%graph(drug,1,4A,A,A10,HEART RATE (b/m),sumto,0,24,HR,mean,
Mean Response Profile,60,95,5,(mins),);
%graph(drug,1,4B,A,A11,HEART RATE (b/m),sumto,0,24,HR,median,
Median Response Profile,60,95,5,(mins),);
%graph(drug,1,4C,A,A12,HEART RATE (b/m),sumto,0,24,HR,min,
Minimum Response Profile,35,75,5,(mins),);
%graph(drug,1,4D,A,A13,HEART RATE (b/m),sumto,0,24,HR,max,
Maximum Response Profile,70,180,10,(mins),);
%graph(drug,1,4A,B,B10,SYSTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,SBP,mean,
Mean Response Profile,115,165,5,(mins),);
%graph(drug,1,4B,B,B11,SYSTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,SBP,median,
Median Response Profile,110,165,5,(mins),);
%graph(drug,1,4C,B,B12,SYSTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,SBP,min,
Minimum Response Profile,80,135,5,(mins),);
%graph(drug,1,4D,B,B13,SYSTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,SBP,max,
Maximum Response Profile,140,205,5,(mins),);
%graph(drug,1,4A,C,C10,DIASTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,DBP,mean,
Mean Response Profile,70,105,5,(mins),);
%graph(drug,1,4B,C,C11,DIASTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,DBP,median,
Median Response Profile,65,110,5,(mins),);
%graph(drug,1,4C,C,C12,DIASTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,DBP,min,
Minimum Response Profile,40,90,5,(mins),);
%graph(drug,1,4D,C,C13,DIASTOLIC BLOOD PRESSURE (mmHg),sumto,0,24,DBP,max,
```

```
Maximum Response Profile,90,145,5,(mins),);
%graph(group,2,4A,D,D10,DIETARY RESPONSE,sumto,0,9,HR,mean,
Mean Response Profile,0.4,1.1,0.1,(mins),);
%graph(group,2,4B,D,D11,DIETARY RESPONSE,sumto,0,9,HR,median,
Median Response Profile,0.1,1.1,0.1,(mins),);
%graph(group,2,4C,D,D12,DIETARY RESPONSE,sumto,0,9,HR,min,
Minimum Response Profile,0.3,0.9,0.1,(mins),);
%graph(group,2,4D,D,D13,DIETARY RESPONSE,sumto,0,9,HR,max,
Maximum Response Profile,0.4,1.3,0.1,(mins),);
%end;
%if &ds=2 %then %do;
%graph(drug,1,22A,A,A10_1,HEART RATE (b/m),sumtg3,1,8,HR,mean,
Mean Response Profile,60,85,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22B,A,A11_1,HEART RATE (b/m),sumtg3,1,8,HR,median,
Median Response Profile,60,85,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22C,A,A12_1,HEART RATE (b/m),sumtg3,1,8,HR,min,
Minimum Response Profile,40,75,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22D,A,A13_1,HEART RATE (b/m),sumtg3,1,8,HR,max,
Maximum Response Profile,80,130,10,GROUP,Mean of 3 hrs);
%graph(drug,1,22A,B,B10_1,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,SBP,mean,
Mean Response Profile,115,165,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22B,B,B11_1,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,SBP,median,
Median Response Profile,115,165,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22C,B,B12_1,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,SBP,min,
Minimum Response Profile,80,135,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22D,B,B13_1,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,SBP,max,
Maximum Response Profile,140,195,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22A,C,C10_1,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,DBP,mean,
Mean Response Profile,70,105,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22B,C,C11_1,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,DBP,median,
Median Response Profile,70,110,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22C,C,C12_1,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,DBP,min,
Minimum Response Profile,45,90,5,GROUP,Mean of 3 hrs);
%graph(drug,1,22D,C,C13_1,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg3,1,8,DBP,max,
Maximum Response Profile,90,130,5,GROUP,Mean of 3 hrs);
%graph(group,2,22A,D,D10_1,DIETARY RESPONSE,sumtg3,1,3,HR,mean,
Mean Response Profile,0.4,1.0,0.1,GROUP,Mean of 3 hrs);
%graph(group,2,22B,D,D11_1,DIETARY RESPONSE,sumtg3,1,3,HR,median,
Median Response Profile,0.1,1.0,0.1,GROUP,Mean of 3 hrs);
%graph(group,2,22C,D,D12_1,DIETARY RESPONSE,sumtg3,1,3,HR,min,
Minimum Response Profile,0.4,0.9,0.1,GROUP,Mean of 3 hrs);
%graph(group,2,22D,D,D13_1,DIETARY RESPONSE,sumtg3,1,3,HR,max,
Maximum Response Profile,0.5,1.1,0.1,GROUP,Mean of 3 hrs);
%graph(drug,1,42A,A,A10_2,HEART RATE (b/m),sumtg2,1,12,HR,mean,
Mean Response Profile,60,95,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42B,A,A11_2,HEART RATE (b/m),sumtg2,1,12,HR,median,
Median Response Profile,60,95,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42C,A,A12_2,HEART RATE (b/m),sumtg2,1,12,HR,min,
Minimum Response Profile,40,75,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42D,A,A13_2,HEART RATE (b/m),sumtg2,1,12,HR,max,
Maximum Response Profile,70,180,10,GROUP,Mean of 2 hrs);
%graph(drug,1,42A,B,B10_2,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,SBP,mean,
Mean Response Profile,115,165,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42B,B,B11_2,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,SBP,median,
Median Response Profile,115,165,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42C,B,B12_2,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,SBP,min,
Minimum Response Profile,80,135,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42D,B,B13_2,SYSTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,SBP,max,
Maximum Response Profile,140,195,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42A,C,C10_2,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,DBP,mean,
Mean Response Profile,70,105,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42B,C,C11_2,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,DBP,median,
Median Response Profile,70,110,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42C,C,C12_2,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,DBP,min,
Minimum Response Profile,45,90,5,GROUP,Mean of 2 hrs);
%graph(drug,1,42D,C,C13_2,DIASTOLIC BLOOD PRESSURE (mmHg),sumtg2,1,12,DBP,max,
Maximum Response Profile,90,130,5,GROUP,Mean of 2 hrs);
 %end;
%mend when;
%when(1,Before);
%when(2,After);
```

```
/*************************************************************************************************
 PROGRAM: ABNPLOT.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-JAN-96
 A set of plots are produced for all data of means and medians of actual data and change from
baseline.
 The frequency of abnormal readings were plotted for each individual patient.
*************************************************************************************************/
libname db '/home/sshanbha/Project/abp/SSDfiles';
libname graph '/home/sshanbha';
options pageno=1;
%include '/home/sshanbha/Project/macros/formats.sas';
%macro when(l,l2,when);
%MACRO PLOT(c,m,no,title,d,tit,n,tn,foot);
filename gsasfile "/home/sshanbha/GIF1/ &no.&l..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.1
        htitle=1.1
        autofeed
        cback=white
        noprompt;

data abn;
     set db.abn&l2;
     where measure="&m";
     *centre=1*(substr(patient,1,1));
run;
proc sort data=abn;
     by centre patient;
run;
data abn;
     set abn;
     if centre="&c" then output;
run;
data abn;
     set abn;
     id=_N_;
run;
symbol1 color=black interpol=none width=0.5 value=dot height=1 line=1;
symbol2 color=black interpol=none width=0.5 value=circle height=1 line=2;
symbol3 color=black interpol=none width=0.5 value=square height=1 line=5;
symbol4 color=black interpol=none width=0.5 value=triangle height=1 line=26;
axis2 label=(h=0.2in angle=90 "NUMBER OF &tn RESULTS") order=(0 to 24 by 1) offset=(2) width=3
c=black;
axis1 label=(h=0.2in "PATIENT") order=(1 to 50 by 1) offset=(2) width=3 c=black;
proc gplot data=abn;
     plot &n*id=drug
     / haxis=axis1 vaxis=axis2 hminor=0 vminor=0 caxis=black frame ctext=black;

     title1 c=black h=2.0 "Number Of &tn Results For &title";
     title2 c=black h=1.5 "&tit: For Centre &c";
     footnote j=l c=black h=1.5 "NOTE: &when &foot";
run;
footnote ' ';
title ' ';
quit;
run;
%MEND PLOT;
%plot(1,HR,AAH1,HEART RATE (B/MIN),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(1,HR,AAN1,HEART RATE (B/MIN),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(1,HR,AAL1,HEART RATE (B/MIN),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%plot(2,HR,AAH2,HEART RATE (B/MIN),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(2,HR,AAN2,HEART RATE (B/MIN),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(2,HR,AAL2,HEART RATE (B/MIN),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%plot(1,SBP,BAH1,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(1,SBP,BAN1,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(1,SBP,BAL1,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%plot(2,SBP,BAH2,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(2,SBP,BAN2,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(2,SBP,BAL2,SYSTOLIC BP (MMHG),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%plot(1,DBP,CAH1,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(1,DBP,CAN1,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(1,DBP,CAL1,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%plot(2,DBP,CAH2,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nh,Abnormally High,missing data replaced);
%plot(2,DBP,CAN2,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nn,Normal,missing data replaced);
%plot(2,DBP,CAL2,DIASTOLIC BP (MMHG),1,ORIGINAL DATA,nl,Abnormally Low,missing data replaced);
%mend when;
%when(_1,1,Before);
*%when(_2,2,After);
```

```
/*************************************************************************************************

 PROGRAM: MEANSE.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-JAN-96
 Individual patient profiles before and after missing data generated.
*************************************************************************************************/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1;
%macro sub(m,title2);
%macro graph(drg,ther,tm,ds,app,fig,fig2,i,no,no2,m2,data,d,t,u2,t2,value,title,time,grp);
%if &ds=1 %then %do;
data GRAPH1(keep=patient drug &t);
     set abp.&data._&m;
     where measure="&i";
run;
%end;
%else %if &ds=2 %then %do;
data GRAPH2(keep=subject group &t);
     set diet.&data._&m;
run;
%end;
data plot;
     set graph&ds;
     array t{&u2} &t;
     do time=1 to &u2;
        value=t{time};
        output;
     end;
     value=.;
     output;
run;
filename gsasfile "/home/sshanbha/GIF1/&no._&m.&m2..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.1
        htitle=1.1
        autofeed
        cback=white
        noprompt;
symbol1 color=black interpol=stdmj value=none line=1;
symbol2 color=black interpol=stdmj value=none line=26;
symbol3 color=black interpol=stdmj value=none line=2;
symbol4 color=black interpol=stdmj value=none line=34;

axis1 label=(h=0.2in "&time") order=(1 to &u2 by 1) offset=(2) width=3;
axis2 label=(h=0.2in angle=90 "&value");

proc gplot data=plot;
   *  title1 c=black h=2.0 "Appendix &app";
   *  title2 c=black h=2.0 "Figure &fig";
     title1 c=black h=1.5 "Group means and standard errors Over &tm for &value data";
     title2 c=black h=1.5 "&title";
     plot value*time=&drg
     / haxis=axis1 vaxis=axis2 hminor=0 vminor=0 caxis=black frame ctext=black;
    footnote j=l c=black h=1.5 "Note: &title2";
run;
footnote ' ';
title ' ';
quit;
run;
%mend graph;
quit;
%if &m=1 %then %do;
%graph(drug,Treatment,Time,1,A,3,,HR,a9,a10,,omult,1,_0-_24,25,26,Heart Rate (beats/min), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,B,3,,SBP,b9,b10,,omult,1,_0-_24,25,26,Systolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,C,3,,DBP,c9,c10,,omult,1,_0-_24,25,26,Diastolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(group,Therapy,Time,2,D,3,,,d9,d10,,omult,1,_0-_9,10,11,Dietary Response, Original Data,TIME+1
(hours),group1);
%end;
%if &m=2 %then %do;
%graph(drug,Treatment,Time,1,A,21,,HR,a9,a10,_1,mgrp3,1,grp1-grp8,8,9,Heart Rate (beats/min),
Average of 3 Time Points,TIME GROUP,);
%graph(drug,Treatment,Time,1,B,21,,SBP,b9,b10,_1,mgrp3,1,grp1-grp8,8,9,Systolic BP (mm/Hg), Average
of 3 Time Points,TIME GROUP,);
%graph(drug,Treatment,Time,1,C,21,,DBP,c9,c10,_1,mgrp3,1,grp1-grp8,8,9,Diastolic BP (mm/Hg), Average
of 3 Time Points,TIME GROUP,);
```

```
%graph(group,Therapy,Time,2,D,21,,,d9,d10,_1,mgrp3,1,grp1-grp3,3,4,Dietary Response, Average of 3
Time Points,TIME GROUP,group1);
%graph(drug,Treatment,Time,1,A,38,,HR,a9,a10,_2,mgrp2,1,grp1-grp12,12,13,Heart Rate (beats/min),
Average of 2 Time Points,TIME GROUP,);
%graph(drug,Treatment,Time,1,B,38,,SBP,b9,b10,_2,mgrp2,1,grp1-grp12,12,13,Systolic BP (mm/Hg),
Average of 2 Time Points,TIME GROUP,);
%graph(drug,Treatment,Time,1,C,38,,DBP,c9,c10,_2,mgrp2,1,grp1-grp12,12,13,Diastolic BP (mm/Hg),
Average of 2 Time Points,TIME GROUP,);
%end;
%mend sub;
%sub(1,Before Missing Data Replaced);
%sub(2,After Missing Data Replaced);
```

```
/*************************************************************************************************

 PROGRAM: IBOXPLOT.SAS
 PROGRAMMER: SHARAYU SHANBHAG
 DATE: 10-JAN-96
 Box plots before and after missing data generated.
*************************************************************************************************/

libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
options pageno=1;
%macro sub(m,title2);
%macro graph(drg,ther,tm,ds,app,fig,fig2,i,no,no2,m2,data,d,t,u2,t2,value,title,time,grp);
%if &ds=1 %then %do;
data GRAPH1(keep=patient drug &t);
     set abp.&data._&m;
     where drug=&d and measure="&i";
run;
%end;
%else %if &ds=2 %then %do;
data GRAPH2(keep=subject group &t);
     set diet.&data._&m;
     where group="&grp";
run;
%end;
data plot;
     set graph&ds;
     array t{&u2} &t;
     do time=1 to &u2;
        value=t{time};
        output;
     end;
     value=.;
     output;
run;
filename gsasfile "/home/sshanbha/GIF1/&no._&m.&m2..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.1
        htitle=1.1
        autofeed
        cback=white
        noprompt;                    * TO THE GIF FILE **;
symbol1 color=black interpol=join value=dot line=1;

axis1 label=(h=0.2in "&time") order=(1 to &t2 by 1) offset=(2) width=3;
axis2 label=(h=0.2in angle=90 "&value");

proc gplot data=plot;
   *  title1 c=black h=2.0 "Appendix &app";
   *  title2 c=black h=2.0 "Figure &fig";
     title1 c=black h=1.5 "Plot of Data Over &tm On &ther &d: &value";
     title2 c=black h=1.5 "&title";
     plot value*time=&drg
     /skipmiss haxis=axis1 vaxis=axis2 hminor=0 vminor=0 caxis=black frame ctext=black nolegend;
     footnote c=black j=l h=1.5 "Note: &title2";
run;
title ' ';
footnote ' ';
%if &m=1 %then %do;
filename gsasfile "/home/sshanbha/GIF1/&no2._&m.&m2..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.1
        htitle=1.1
        autofeed
        cback=white
        noprompt;                              * TO THE GIF FILE **;
axis1 label=(h=0.2in "&time") order=(1 to &u2 by 1) offset=(1);
axis2 label=(h=0.2in angle=90 "&value");

proc gplot data=plot;
   *  title1 c=black h=2.0 "Appendix &app";
   *  title2 c=black h=2.0 "Figure &fig2";
     title1 c=black h=1.5 "Box plot of Data Over &tm On &ther &d: &value";
     title2 c=black h=1.5 "&title";
     plot value * time=&drg
```

```
     / haxis=axis1 vaxis=axis2 hminor=0 vminor=0 caxis=black frame ctext=black nolegend;
     symbol ci=black interpol=boxt00;
    footnote1 j=l c=black h=1.5 "Box plots show range, quartiles and median";
    footnote2 j=l c=black h=1.5 "Note: &title2";
run;
footnote ' ';
title ' ';
quit;
run;
%end;
%mend graph;
quit;
%if &m=1 %then %do;    ** Original DATA **;
%graph(drug,Treatment,Time,1,A,1A,2A,HR,a1,a5,,omult,1,_0-_24,25,26,Heart Rate (beats/min), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,A,1B,2B,HR,a2,a6,,omult,2,_0-_24,25,26,Heart Rate (beats/min), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,A,1C,2C,HR,a3,a7,,omult,3,_0-_24,25,26,Heart Rate (beats/min), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,A,1D,2D,HR,a4,a8,,omult,4,_0-_24,25,26,Heart Rate (beats/min), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,B,1A,2A,SBP,b1,b5,,omult,1,_0-_24,25,26,Systolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,B,1B,2B,SBP,b2,b6,,omult,2,_0-_24,25,26,Systolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,B,1C,2C,SBP,b3,b7,,omult,3,_0-_24,25,26,Systolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,B,1D,2D,SBP,b4,b8,,omult,4,_0-_24,25,26,Systolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,C,1A,2A,DBP,c1,c5,,omult,1,_0-_24,25,26,Diastolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,C,1B,2B,DBP,c2,c6,,omult,2,_0-_24,25,26,Diastolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,C,1C,2C,DBP,c3,c7,,omult,3,_0-_24,25,26,Diastolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(drug,Treatment,Time,1,C,1D,2D,DBP,c4,c8,,omult,4,_0-_24,25,26,Diastolic BP (mm/Hg), Original
Data,TIME+1 (hours),);
%graph(group,Therapy,Time,2,D,1A,2A,,d1,d4,,omult,1,_0-_9,10,11,Dietary Response, Original
Data,TIME+1 (hours),group1);
%graph(group,Therapy,Time,2,D,1B,2B,,d2,d5,,omult,2,_0-_9,10,11,Dietary Response, Original
Data,TIME+1 (hours),group2);
%graph(group,Therapy,Time,2,D,1C,2C,,d3,d6,,omult,3,_0-_9,10,11,Dietary Response, Original
Data,TIME+1 (hours),group3);
%end;
%else %if &m=2 %then %do; ** After Data Replaced **;

%graph(drug,Treatment,Grouped Time,1,A,21A,,HR,a1,,_2,mgrp3,1,grp1-grp8,8,9,Heart Rate (beats/min),
Grouped Data: Mean of 3 hrs,TIME
 GROUP);
%graph(drug,Treatment,Grouped Time,1,A,21B,,HR,a2,,_2,mgrp3,2,grp1-grp8,8,9,Heart Rate (beats/min),
Grouped Data: Mean of 3 hrs,TIME
 GROUP);
%graph(drug,Treatment,Grouped Time,1,A,21C,,HR,a3,,_2,mgrp3,3,grp1-grp8,8,9,Heart Rate (beats/min),
Grouped Data: Mean of 3 hrs,TIME
 GROUP);
%graph(drug,Treatment,Grouped Time,1,A,21D,,HR,a4,,_2,mgrp3,4,grp1-grp8,8,9,Heart Rate (beats/min),
Grouped Data: Mean of 3 hrs,TIME
 GROUP);
%graph(drug,Treatment,Grouped Time,1,B,21A,,SBP,b1,,_2,mgrp3,1,grp1-grp8,8,9,Systolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME GROUP
,);
%graph(drug,Treatment,Grouped Time,1,B,21B,,SBP,b2,,_2,mgrp3,2,grp1-grp8,8,9,Systolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME GROUP
,);
%graph(drug,Treatment,Grouped Time,1,B,21C,,SBP,b3,,_2,mgrp3,3,grp1-grp8,8,9,Systolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME GROUP
,);
%graph(drug,Treatment,Grouped Time,1,B,21D,,SBP,b4,,_2,mgrp3,4,grp1-grp8,8,9,Systolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME GROUP
,);
%graph(drug,Treatment,Grouped Time,1,C,21A,,DBP,c1,,_2,mgrp3,1,grp1-grp8,8,9,Diastolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,21B,,DBP,c2,,_2,mgrp3,2,grp1-grp8,8,9,Diastolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,21C,,DBP,c3,,_2,mgrp3,3,grp1-grp8,8,9,Diastolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,21D,,DBP,c4,,_2,mgrp3,4,grp1-grp8,8,9,Diastolic BP (mm/Hg),
Grouped Data: Mean of 3 hrs,TIME
 GROUP,);
%graph(group,Therapy,Grouped Time,2,D,21A,,,d1,,_2,mgrp3,1,grp1-grp3,3,4,Dietary Response, Grouped
Data: Mean of 3 hrs,TIME GROUP,
group1);
%graph(group,Therapy,Grouped Time,2,D,21B,,,d2,,_2,mgrp3,2,grp1-grp3,3,4,Dietary Response, Grouped
Data: Mean of 3 hrs,TIME GROUP,
```

```
group2);
%graph(group,Therapy,Grouped Time,2,D,21C,,,d3,,_2,mgrp3,3,grp1-grp3,3,4,Dietary Response, Grouped
Data: Mean of 3 hrs,TIME GROUP,
group3);
%graph(drug,Treatment,Grouped Time,1,A,41A,,HR,a1,,_1,mgrp2,1,grp1-grp12,12,13,Heart Rate
(beats/min), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,A,41B,,HR,a2,,_1,mgrp2,2,grp1-grp12,12,13,Heart Rate
(beats/min), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,A,41C,,HR,a3,,_1,mgrp2,3,grp1-grp12,12,13,Heart Rate
(beats/min), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,A,41D,,HR,a4,,_1,mgrp2,4,grp1-grp12,12,13,Heart Rate
(beats/min), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,B,41A,,SBP,b1,,_1,mgrp2,1,grp1-grp12,12,13,Systolic BP (mm/Hg),
Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,B,41B,,SBP,b2,,_1,mgrp2,2,grp1-grp12,12,13,Systolic BP (mm/Hg),
Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,B,41C,,SBP,b3,,_1,mgrp2,3,grp1-grp12,12,13,Systolic BP (mm/Hg),
Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,B,41D,,SBP,b4,,_1,mgrp2,4,grp1-grp12,12,13,Systolic BP (mm/Hg),
Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,41A,,DBP,c1,,_1,mgrp2,1,grp1-grp12,12,13,Diastolic BP
(mm/Hg), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,41B,,DBP,c2,,_1,mgrp2,2,grp1-grp12,12,13,Diastolic BP
(mm/Hg), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,41C,,DBP,c3,,_1,mgrp2,3,grp1-grp12,12,13,Diastolic BP
(mm/Hg), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%graph(drug,Treatment,Grouped Time,1,C,41D,,DBP,c4,,_1,mgrp2,4,grp1-grp12,12,13,Diastolic BP
(mm/Hg), Grouped Data: Mean of 2 hrs,TIME
 GROUP,);
%end;
%mend sub;
%sub(1,Before Missing Data Replaced);
%sub(2,After Missing Data Replaced);
```

```
/*************************************************************************************************************
***

HISTPLOT.SAS
Programmer: Sharayu Shanbhag
Date: 06/JAN/97

Produces Histograms for Each variable mean, median, min, max, q1 and q3.
         Also for overall summaries.

*************************************************************************************************************
***/
libname abp '/home/sshanbha/Project/abp/SSDfiles';
libname diet '/home/sshanbha/Project/diet/SSDfiles';
%include '/home/sshanbha/Project/macros/formats.sas';
%macro when(l,when);
%macro perm(v,perm);
%macro hist(trt,drg,n1,n2,data,t,var,tit,form,f,av,m);
%if &v=1 %then %do;
data a;
     set &perm..&data.&l;
     a=round(&t,0.1);
    *b=round(&t,1.0);
   *  format a &form;
run;
%end;
%if &v=2 %then %do;
data a;
     set &perm..&data.&l;
     a=round(&t,0.1);
    *b=round(&t,1.0);
run;
%end;
filename gsasfile "/home/sshanbha/GIF1/ &n1.&l.&m..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.5
        htitle=2.0
        autofeed
        cback=white
        noprompt;

pattern1 value=l3 c=black;
proc gchart data=a;
     title1 c=black h=1.5 "Block Charts of Overall &tit Values";
     title2 c=black h=1.5 "&av";
     block a / noheading ctext=black coutline=black caxis=black;
     label a="&tit";
run;
footnote "Note: &when &f";
quit;
footnote ' ';
title ' ';

filename gsasfile "/home/sshanbha/GIF1/ &n2.&l.&m..gif";
goption reset=all
        display
        device=imggif
        gaccess=gsasfile
        rotate=landscape
        ftext=swiss
        ftitle=swiss
        htext=1.5
        htitle=2.0
        cback=white
        autofeed
        noprompt;
pattern1 value=l3 c=black;

proc gchart data=a;
     title1 c=black h=1.5 "Block Charts of Overall &tit Values by &trt";
     title2 c=black h=1.5 "&av";
     block a / group=&drg noheading ctext=black coutline=black caxis=black ;
     label a= "&tit";
run;
footnote "Note: &when &f";
quit;
%mend hist;
footnote ' ';
title ' ';
quit;
```

```
%if &v=1 %then %do;
%hist(Treatment,drug,hc1,hc2,sumpo,Base,DBP,Baseline Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc3,hc4,sumpo,Change,DBP,Change in Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc5,hc6,sumpo,Mean,DBP,Mean Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc7,hc8,sumpo,Median,DBP,Median Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc9,hc10,sumpo,Min,DBP,Minimum Diastolic BP (mm/Hg),onete.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc11,hc12,sumpo,Max,DBP,Maximum Diastolic BP (mm/Hg),twote.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc13,hc14,sumpo,q1,DBP,Lower Quartile Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Original Data,);
%hist(Treatment,drug,hc15,hc16,sumpo,q3,DBP,Upper Quartile Diastolic BP (mm/Hg),onee.,Missing Data
Replaced,Original Data,);

%hist(Treatment,drug,hc1,hc2,sumpg3,Change,DBP,Change in Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc3,hc4,sumpg3,Mean,DBP,Mean Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc5,hc6,sumpg3,Median,DBP,Median Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc7,hc8,sumpg3,Min,DBP,Minimum Diastolic BP (mm/Hg),onete.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc9,hc10,sumpg3,Max,DBP,Maximum Diastolic BP (mm/Hg),twote.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc11,hc12,sumpg3,q1,DBP,Q1 Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc13,hc14,sumpg3,q3,DBP,Q3 Diastolic BP (mm/Hg),onee.,Missing Data
Replaced,Average of 3 Time Points,_1);
%hist(Treatment,drug,hc1,hc2,sumpg2,Change,DBP,Change in Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc3,hc4,sumpg2,Mean,DBP,Mean Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc5,hc6,sumpg2,Median,DBP,Median Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc7,hc8,sumpg2,Min,DBP,Minimum Diastolic BP (mm/Hg),onete.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc9,hc10,sumpg2,Max,DBP,Maximum Diastolic BP (mm/Hg),twote.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc11,hc12,sumpg2,q1,DBP,Q1 Diastolic BP (mm/Hg),twoe.,Missing Data
Replaced,Average of 2 Time Points,_2);
%hist(Treatment,drug,hc13,hc14,sumpg2,q3,DBP,Q3 Diastolic BP (mm/Hg),onee.,Missing Data
Replaced,Average of 2 Time Points,_2);
%end;
%if &v=2 %then %do;
%end;
%mend perm;
%perm(1,abp);
%perm(2,diet);
%mend when;
%when(_1,Before);
%when(_2,After);
```